EFFECTS OF INHALED PARTICLES ON HUMAN HEALTH:

INFLUENCE OF PARTICLE SIZE AND SHAPE

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PUBLICATION

EFFECTS OF INHALED PARTICLES ON HUMAN HEALTH: INFLUENCE OF PARTICLE SIZE AND SHAPE

Particles having a diverse range of physical and chemical properties may be emitted into the atmospheric environment from natural processes and from the activities of man. The inhalation by man of certain of these airborne particles may under some circumstances pose a risk to health. Paramount to the interpretation of the results of studies on health effects is an understanding of the behavior of particles in the human respiratory system.

This document examines the role of size and shape of particles with respect to their entry into the respiratory system, and the resulting adverse human health effects. It was prepared to evaluate the scientific criteria pertaining to the effect of particle size and shape on health, and also to identify critical gaps in knowledge. The authors recommend that: (i) the size, shape and chemical composition of particles be considered in all investigations of causal relationships between exposure to particles and human health effects; (ii) studies of regional deposition and clearance of particles more closely reflect exposure conditions in the community; and (iii) studies be made of specific human health effects which can be related to well-characterized exposures to airborne particles in order to elucidate the influence of particle size and shape upon health.

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PUBLICATION

EFFETS SUR LA SANTE DES PARTICULES ABSORBEES PAR VOIE RESPIRATOIRE: INFLUENCE DE LEUR TAILLE ET DE LEUR FORME

Des particules ayant toute une gamme de propriétés physiques et chimiques peuvent être émises dans l'atmosphère par les processus naturels et les activités de l'homme. Il peut y avoir des risques pour la santé si certaines de ces particules en suspension entrent par voie respiratoire dans l'organisme humain, dans certaines conditions. Pour bien interpréter les résultats des études concernant les effets sur la santé, il est primordial de comprendre le comportement des particules dans le système respiratoire humain.

Dans cette publication, on examine le rôle de la taille et de la forme des particules qui pénètrent dans le système respiratoire, et les effets nocifs sur l'homme. Le document a pour but d'évaluer les critères scientifiques pertinents et aussi d'identifier les lacunes importantes dans nos connaissances actuelles. Les auteurs recommandent donc: (i) que l'on tienne compte de la taille, la forme et la composition chimique des particules lors de toute investigation des rapports entre l'exposition aux particules et leurs effets sur la santé, (ii) que les études du dépôt local et de la clearance des particules reflètent mieux les conditions d'exposition dans la communauté en question, et (iii) que l'on étudie les effets spécifiques sur la santé qui peuvent être mis en rapport avec des expositions bien caractérisées aux particules en suspension afin d'élucider l'influence de leur taille et de leur forme sur la santé.

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PANEL ON INHALED PARTICLES

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SUMMARY

Particles having a diverse range of physical and chemical properties may be emitted into the atmospheric environment as a result of the activities of both nature and man. The inhalation by man of certain of these airborne particles may under some circumstances pose a risk to health. Paramount to the interpretation of the results of studies on health effects is an understanding of a particle's behavior in the human respiratory system.

This document examines the role that the size and shape of particles play in their ability to enter the respiratory system and cause adverse human health effects. Much of the information relating particle size and shape to health effects has been derived from studies of silica, talc, fibrous glass, and asbestos; these substances are not exhaustively documented in this report, but instead have been used as bases for an examination of any causal relationships between particle size and shape and observed health effects. Other documents (cf. Shugar 1979) examine the individual substances. A companion document on airborne particles (NRCC 1982) examines the effects of aerosols on optical properties of the atmosphere, clouds, fogs, precipitation, atmospheric electricity, and climate.

1. NATURE AND SIZE AND SHAPE CHARACTERISTICS OF AIRBORNE PARTICLES (see Chapter 2)

The human respiratory system is the primary route for human exposure to airborne particles. Since the retention of inhaled particles and their associated health effects are, in part, dependent upon the size and shape of the particles, the measurement of concentration and size and shape characteristics of particles is essential to any investigation of the causal relationships between exposure and health effects. A relatively complex and often conflicting terminology has appeared in the literature with respect to the study of airborne particles. In addition, many of the data that are available are biased towards the type of measurement method employed (for further discussion, refer to NRCC (1982)).

The most important general parameter used for the characterization of airborne particles is particle size. The size of spherical particles may be rigorously defined by measurement of particle diameter. However, because most airborne particles are not spherical, a variety of empirical parameters have been proposed to define particle size and shape which are correlated with particle behavior in air. For highly nonspherical particles (e.g. fibers), the measurement of particle size is more complex since diameter, length, and shape are all important when attempting to characterize particle behavior. In the atmosphere, many particles do not exist singly but instead are agglomerates or aggregates of particles; many collection methods alter such assemblages and hence do not provide a true measure of particle size from the standpoint of human respirability. With respect to the study of the entry and deposition of particles in the respiratory system, the measurement of aerodynamic diameter is considered to be appropriate, as it permits the comparison of the depositional sites of particles of equivalent aerodynamic diameter.

The majority of natural and man-made aerosols possess a significant degree of polydispersity with respect to particle size. As a result, the measurement of mean particle size alone is seldom sufficient to describe the true behavior of a polydisperse system, and it is therefore also necessary to determine particle size distribution.

2. DEPOSITION, CLEARANCE, AND RETENTION OF INHALED PARTICLES IN THE RESPIRATORY SYSTEM (see Chapter 3)

The ability of particles to initiate biological reactions in the lung or produce systemic reactions in the human body is a function of their mode of entry into the respiratory system, site of deposition and retention, rate of absorption or translocation, and biological activity. Evidence suggests that particle size distribution, shape, density, surface area, electrostatic charge, hygroscopicity, deliquescence, and chemical composition play significant roles in the above processes.

DEPOSITION

The penetration and deposition of particles in the respiratory system are dependent upon the anatomy of the respiratory tract, physiological factors such as breathing pattern, airflow dynamics, etc., and physical properties of the particles. Spherical particles may be deposited by several mechanisms, of which the following are considered to be the most important: (i) impaction - dependent upon particle size and density, and the primary deposition mechanism in the upper respiratory tract for particles larger than 1-2 μm in aerodynamic diameter; (ii) gravitational settling - dependent upon particle size and density, and important for deposition of particles larger than about 0.1 μm in the tracheobronchial and pulmonary regions of the respiratory system; and (iii) diffusion (Brownian movement) - important for particles smaller than about 0.5 μm. For highly nonspherical particles (e.g. fibers, length/breadth ratio >3:1), interception at the branching points of the respiratory system becomes important, and is dependent upon fiber length. Interception is an important method for removing particles from the airstream before they reach the pulmonary region. Fiber diameter is a major determining factor in gravitational settling, explaining the presence in lung tissue of fibers as long as 200 μm.

The penetration and deposition of spherical particles in the respiratory system have been well studied in both animals and man. Total deposition increases with increasing aerodynamic diameter for particles larger than about 0.5 μm. Approximately 90% of the particles of 5-μm diameter are deposited. Nose breathing and mouth breathing lead to somewhat different depositional patterns; for nose breathing, total deposition essentially occurs for 5-μm particles, while for mouth breathing, total deposition occurs for particles of approximately 10 μm. For particles smaller than 0.5 μm, total deposition increases with decreasing particle diameter.

Since deposition, clearance, and biological effects vary in different parts of the respiratory system, it is important to examine the regional deposition of particles. Particles larger than 10 μm in aerodynamic diameter are preferentially removed in the nasopharyngeal region of the respiratory system. Studies have shown that 30-65% of particles between 1.1 and 4.6 μm in diameter are deposited in the nonciliated anterior naris. Approximately 45% of particles 2-10 μm in diameter are deposited in the anterior portion of the nasal airways. In the tracheobronchial region, deposition is low for particles <3.5 μm and increases rapidly as aerodynamic diameter increases to 12.2 μm. For particles in the size range 0.2-5 μm, pulmonary deposition varies between 20 and 60%, with maximum deposition occurring for particles approximately 1.2 μm in diameter. As particle diameter decreases below the submicrometre level, diffusional deposition becomes important, and a second maximum in pulmonary deposition occurs for particles <0.1 μm in diameter.

With the exception of animal and model studies on asbestos and glass fibers, there is little information available regarding the respiratory deposition or aerodynamic properties of particles that deviate from sphericity. There is general agreement that the aerodynamic properties (e.g. settling rate) of fibers are dependent upon actual fiber diameter, with fiber length being of only secondary importance. The deposition of such particles in the respiratory system is related to their aerodynamic diameter, and relatively long fibers having a small aerodynamic diameter may therefore be deposited in the lower regions of the respiratory tract. Very little information is available on the effects of particle geometry on deposition. It appears that curved or curly fibers are deposited higher in the respiratory tract than are straight ones. Fiber length appears to be the determining factor when comparing the deposition of straight fibers, curved fibers, and fiber aggregates; however, in the studies examined, experimental design may have been biased towards fiber length and masked secondary effects due to geometry.

Regional deposition of particles is governed not only by a particle's physical properties but also by physiological parameters. There is an increased penetration of the respiratory system for mouth breathers compared with nose breathers. Slow, deep breathing results in greater deposition than does fast, shallow breathing; this difference is more pronounced for 1.6-μm particles than for 0.14-μm particles. The health of a subject is also an important parameter affecting deposition, with tracheobronchial deposition being enhanced at the expense of pulmonary deposition in diseased and obstructed lungs. Because children have, on average, smaller airways and a higher metabolic rate, penetration and deposition are expected to be enhanced.

CLEARANCE

Once deposited, inhaled particles may be removed from their initial site of deposition by processes that are dependent upon site of deposition and certain particle characteristics. It is generally accepted that there are two clearance phases, rapid and long-term. It is important to recognize that the respiratory system not only is the primary site of particle deposition but also provides a route for the translocation of particles to other organs where they may elicit adverse biological responses.

In general, the degree of physiological and/or pathological response seems to be related to the rate of removal of deposited particles from the respiratory system. The biological effects of inhaled irritant substances which produce a rapid response may depend more on the quality of the substances initially deposited than on the rate of clearance. Alternatively, materials that produce harmful effects only after long periods of exposure or a long latent interval may exhibit activity only if the material remains in the body long enough to cause pathological damage. In such a case, the quantity of material initially deposited may be of relatively minor importance, assuming that the initial dose is not high enough to impede the clearance mechanisms.

Different clearance mechanisms operate in different regions of the respiratory tract, so that the rate of clearance of a deposited particle will depend not only upon its physical and chemical properties but also upon the site of initial deposition. Particles deposited in the nasopharyngeal and tracheobronchial regions of the respiratory system are usually rapidly removed. Particle size, shape, chemical properties, and site of deposition determine the length of time particles are retained in the nose and influence the particle's ability to produce adverse biological reactions. Although little information is available on retention times of particles deposited in the nose, evidence suggests that particles may be retained for long periods in some portions of the nasal passages. Perforation of the nasal septum has been found in potash miners, and increased risks of nasal tumors among woodworkers and nickel refiners have been reported.

Particles deposited in the tracheobronchial region are removed primarily by mucociliary transport; such transport removes particles to the pharynx where they are swallowed or expectorated. The rate of transport appears to be independent of particle size or shape, except where particles have sufficiently smooth surfaces so that mucus flows around them. The gastrointestinal dose of particles is increased by the translocation of particles from the respiratory tract.

The major rapid clearance mechanism in the pulmonary region is that involving recruitable macrophages. The macrophage output in the pulmonary region is affected by particle size, chemical composition, and total particle load. For submicrometre particles, smaller particles stimulate macrophage response more than larger particles. Phagocytosis is influenced by particle shape, and hence particle clearance from the alveolar surface is affected. Studies have shown that short fibers (<5 μm in length) are rapidly and quantitatively engulfed by macrophages, whereas long fibers (>20 μm in length) are never completely engulfed. Particles of intermediate length (5-20 μm) are sometimes engulfed. Although the site of deposition is governed by particle diameter, it appears that, once the fiber is deposited, its length is the major determining factor with respect to retention in the lung. No differences in the rates of retention in the lung of straight or curved fibers or fiber aggregates were observed in the studies examined, although fiber length may have masked any secondary effects.

As with other adaptive responses, the mechanism for removal of particles by phagocytosis can become saturated. Particles may become sequestered by a tissue reaction or become bound to protein material in the lung. While it has been shown that particles are present in the parietal pleura of the lung, the mechanisms of migration or penetration to the pleural surface are not understood. Hypotheses range from direct penetration through the tissues to lymphatic drainage.

Factors such as inhalation of coexisting gases and vapors, multiple exposures, smoking, infections, and impaired respiratory function may all significantly modify regional deposition and clearance and hence affect retention.

3. TISSUE RESPONSE TO INHALED PARTICLES (see Chapter 4)

Once deposited, a particle's ability to provoke a tissue response which may, in turn, result in adverse health effects is dependent upon the physical and chemical characteristics of the particle and the receptor. It is at the tissue response level that particle composition as well as size and shape become critical.

In general, there are three basic mechanisms by which inhaled particles may evoke a biological response in the respiratory system: (i) a particle, because of its physical and/or chemical nature, may be inherently toxic; (ii) a particle may be chemically inert, but by its physical presence in the lung may modify the clearance of toxic materials contained in other deposited particles; and (iii) a particle may act as a carrier for gases or vapors which are toxic.

With respect to biological response, insoluble inhaled particles are classified as fibrogenic or nonfibrogenic (inert or nuisance). Fibrogenic particles are considered to give rise to lung diseases classified as pneumoconioses. Most of the information currently available on the biological response to particles, *per se*, is derived from industrial exposures. Most of these data are derived from studies using silica, platelike particles (e.g. talc, mica), and fibrous material (e.g. asbestos, fibrous glass).

From the information available, particle size and shape play a significant role in tissue damage due to their inhalation. For example, the inherent tissue-damaging capacity of silica particles increases as particle size decreases. Current theories of the toxic action of silica particles envision that the effects take place at the surface of the particle.

Although little information concerning them is available, platelike particles less than 5 µm in diameter are responsible for biological response. It appears that the chemistry and mineralogy of the particles are important in fibrosis. The data suggest that platy talc produces minimal cell toxicity, but when contaminated with significant amounts of either silica or other cytotoxic materials, it causes a tissue response related to the cytotoxic contaminants rather than to the talc particles themselves.

The role of particle size and shape in tissue response has been more thoroughly studied for fibrous particles such as asbestos. The consequences of asbestos fiber inhalation and retention in the human lung are fibrosis, bronchogenic carcinoma, mesothelioma of the pleura and peritoneum, and carcinoma of the gastrointestinal tract and possibly of other sites such as the larynx. The physical and mechanical characteristics of asbestos fibers are more responsible for their cytotoxicity and fibrogenicity than are their chemical compositions or molecular structures. Long fibers (>20 µm in length) are more fibrogenic than short ones (<5 µm in length) because the long fibers are not as well phagocytosed by macrophages and may be translocated. Until recently, little attention was paid to the possible importance of particle size and shape in carcinogenesis; most carcinogens were considered to act by direct chemical action or by interference with enzyme systems and cell metabolism. However, studies with asbestos have suggested that particle size and shape play an important role, whereas chemical composition is a minor factor. Fibers 20-200 µm in length and 0.5-5 µm in diameter were found to be more effective in inducing mesothelioma than either shorter or longer fibers. Other studies have shown that fibers greater than 8 µm in length and less than or equal to 1.5 µm in diameter had the highest carcinogenic potential; increasing fiber length and decreasing fiber diameter were related to carcinogenicity. In studies with glass fibers, it has been shown that physical characteristics determine tissue damage, with fiber length playing the dominant role. Very recent experimental studies with fibers of the mineral erionite show that, in some areas, long fibers which have very narrow diameters are particularly carcinogenic when in contact with the pleura.

4. HEALTH EFFECTS OF INHALED PARTICLES (see Chapter 5)

Ambient air pollutants in high concentrations have been shown to increase mortality and cause exacerbations of preexisting diseases; however, epidemiological information to date does not provide any direct evidence that the size and shape of airborne particles commonly present in community air are important in the production of health effects.

Although numerous epidemiological studies have been conducted in an attempt to determine both qualitative and quantitative relationships between air pollution and health effects, many of the studies have had limitations. First, there has been an inadequate characterization of ambient air quality parameters used to estimate exposure. Most of the epidemiological studies have relied upon air monitoring data collected with sampling networks whose original design did not include health-related research. Second, there has been an inadequate characterization of health effects. Although a variety of health-related measurements have been utilized, they lack the specificity necessary to measure effects due to particle size and shape. Third, the observed health effects have not been adequately related to specific parameters of community exposure conditions. For example, it has been difficult to distinguish between health effects due to airborne particles and those due to coexisting pollutants such as sulfur dioxide. As a result of these limitations, epidemiological studies may be useful in demonstrating associations but not necessarily in identifying the specific parameters responsible for the health effects. It is evident that the probability of demonstrating a relationship between ambient air pollution and nonspecific health effects is low. Without such measurable health effects, the studies of the size and shape characteristics of ambient particles are not likely to provide any new insights into the community health effects of airborne particles.

Because of the complexities of defining specific health effects in the general population, the majority of information pertaining to the influence of particle size and shape on health has been derived mainly from the study of occupational groups. In the occupational setting, exposures are usually better defined than those of the general population. However, only a relatively healthy segment of the population is usually exposed. Increasingly, focus is being directed at the study of health effects in the families of workers.

There is evidence to indicate that size and shape of highly nonspherical particles (e.g. fibers) play an important role in health effects in the occupational setting and probably in the community. Mesothelioma has been occupationally linked to exposure to several types of asbestos fibers, and experimental evidence suggests that sufficiently durable long (>10 µm) fibers of narrow (<0.5 µm) diameter can produce this tumor. The differences in diameter of fibers in different occupational settings may be a major factor in delineating the risk of mesothelioma for different occupational groups. Measurements of ambient fiber concentrations in Canada are extremely limited, but surveys of mesothelioma occurrence have demonstrated a rate of 1-2 per million population; most of these cases have been linked to direct occupational exposure, although some have been associated with domestic exposure.

The limited data on fibers in the lungs of children suggest that the concentrations per gram of lung tissue may be as high as or even higher than those in adult lung tissue. With respect to lung cancer risks associated with exposure to particles of specific size and shape, a preliminary study in Quebec of persons living in asbestos-mining towns and a study of persons living near an asbestos factory in the United States show virtually no increased mortality for persons not occupationally exposed to asbestos fibers.

RECOMMENDATIONS

This document was prepared for the purposes of developing and evaluating the scientific criteria on the influence of particle size and shape on the health effects of inhaled particles and of identifying critical gaps in knowledge. The available criteria are insufficient to provide anything more than a general assessment of the role of inhaled particle size and shape. The following is a list of recommendations that should be addressed:

1. It is generally recognized that inhaled particles are deposited in various regions of the human respiratory system, partly as a function of particle size and shape. In addition, particle size, shape, chemical composition, etc., affect the rate and degree of particle clearance from the respiratory system and hence particle retention. Since retention of inhaled particles and, consequently, potential health effects are partially dependent upon these characteristics, it is recommended that:

> THE MEASUREMENT OF SIZE, SHAPE, AND CHEMICAL COMPOSITION OF PARTICLES BE CONSIDERED ESSENTIAL TO ANY INVESTIGATION OF CAUSAL RELATIONSHIPS BETWEEN EXPOSURE TO PARTICLES AND HUMAN HEALTH EFFECTS. EMPHASIS SHOULD BE PLACED ON THE STUDY OF REALISTIC SIZES, SHAPES, AND CONCENTRATIONS THAT REFLECT ACTUAL EXPOSURE CONDITIONS IN SELECTED LOCALES.

2. Factors other than airborne particle characteristics affect deposition, clearance, retention, and, hence, health outcome. The effects of modifying factors such as age, health status, cigarette smoking, exposure to other airborne pollutants, etc., need to be considered when conducting experimental studies. It is therefore recommended that:

> STUDIES OF REGIONAL DEPOSITION AND CLEARANCE OF PARTICLES MORE CLOSELY REFLECT EXPOSURE CONDITIONS IN THE COMMUNITY. REPRESENTATIVE SAMPLES OF THE POPULATION CONSIDERED TO BE MOST AT RISK SHOULD BE EXAMINED.

3. While the response of the lung and other tissues to the general presence of particles has been reasonably well studied, the influence of particle size and shape has not received adequate consideration. Tissue reactions may be highly dependent upon particle size and shape, and it is likely that many of the anomalies in experimental results are due to deficiencies in the size and shape characterization of the particles studied. It is therefore recommended that:

> AEROSOLS USED IN EXPERIMENTAL STUDIES OF TISSUE RESPONSE BE PHYSICALLY AND CHEMICALLY CHARACTERIZED SO THAT THE INFLUENCE OF PARTICLE PROPERTIES ON TISSUE RESPONSE MAY BE EXAMINED IN DETAIL.

4. Because the average concentrations of pollutants in community air are usually at levels where methods for detecting and measuring health effects lack sensitivity and specificity, it has been difficult to relate quantitatively particle loading in the community to general health effects. Without a readily measurable health effect, the study of size and shape characteristics of ambient particles is not likely to provide any new insights into the community health effects of inhaled particles. It is therefore recommended that:

> THE STUDY OF SPECIFIC HUMAN HEALTH EFFECTS WHICH CAN BE RELATED TO WELL-CHARACTERIZED EXPOSURES TO AIRBORNE PARTICLES SHOULD BE ENCOURAGED IN ORDER TO ELUCIDATE THE INFLUENCE OF PARTICLE SIZE AND SHAPE UPON HEALTH EFFECTS. HYPOTHESES BASED ON EXPERIMENTAL DATA MAY BE TESTED IN SPECIFIC OCCUPATIONAL GROUPS OR SUBGROUPS OF THE GENERAL POPULATION CONSIDERED TO BE AT RISK WHEN EXPOSED TO CERTAIN TYPES OF PARTICLES. THE RESULTS OF SUCH STUDIES MAY THEN PROVIDE A FIRM BASIS FOR DESIGNING REPRESENTATIVE COMMUNITY HEALTH STUDIES.

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1.0 INTRODUCTION

Ambient air pollution consists of a complex mixture of gases, vapors, and aerosols (solid and liquid particles) which vary in concentration, chemical composition, and physical characteristics with source, time, and location. While it has long been recognized that a knowledge of the size characteristics of airborne particles is likely to be as important as that of chemical composition in understanding the health effects of airborne particles in industry, only recently has much attention been given to the influence of size and shape of particles on community health effects.

The main reason for the upsurge of interest in the size and shape of particles is probably related to two developments over the last 10-20 years. First, technological advances have made it possible to examine and chemically analyze particles which were previously not visible using light optical systems. Instrumentation is now available which permits the chemical analysis of single submicrometre particles and the study of their surface characteristics. Second, certain of the health effects of asbestos had implications for persons not occupationally exposed, and this stimulated the concern of the public and governments as to the community health effects of asbestos fibers.

It is now reasonably well accepted that elevated concentrations of airborne particles in the community can influence health. The excesses in mortality in London, England, during the smogs of 1952 and 1964 clearly showed an association between increased levels of certain types of air pollutants and mortality. Nevertheless, the excess deaths were mainly in young children, the elderly, and persons with preexisting respiratory problems; the possibility that infections played a role cannot be ruled out, and it is not definitely known whether particles or gases played the major role in the outcome. While pointing to the obvious need to control air pollution, the etiology and mechanisms for the health effects remain unknown.

The fact that air pollution has been shown to exacerbate previous or existing health effects and to affect certain more susceptible persons (elderly, infants, and the clinically ill) more seriously raises questions as to whether components of air pollution can produce a primary effect. The need for very high concentrations of pollutants or for susceptible populations in order to readily detect health effects is a problem inherent in most studies of community air pollution. If an agent which causes a specific health effect can be identified in community air, the interpretation of results of studies to determine its effects is relatively straightforward. However, usually the concern is with measures of change or deviations from "normality" in populations which are exposed to a complex mixture of pollutants. Health effects are defined differently in different studies, even where similar techniques of measuring the effects are used. The signs, symptoms, and health effects (e.g. chronic bronchitis, lung cancer) which are likely to be associated with exposure to the broad range of environmental pollutants in community air can result, and often do, from noncommunity exposures (e.g. occupation, hobbies, smoking).

Similar problems exist in unraveling the role played by air pollutants in the exacerbation of preexisting diseases such as chronic bronchitis. Do particles alone play a role or do gases and particles combine for the effect? Virtually all studies to relate levels of air pollutants to adverse health effects suffer from inadequate or extremely crude measurements of the quantity and quality of particles in the air, as well as the existence of many other confounding variables such as smoking, socioeconomic factors, occupation, infections, and seasonal effects. The explanation of urban-rural or intercity differences in lung cancer, chronic bronchitis, hospital admissions, bronchiolitis in children, bronchial asthma, and others, is complicated by the range of other factors which must be taken into account, such as smoking habits, age distributions, infectious agents, diets, occupations, lifestyles, hours of sunlight, and other parameters which differ between the country and the city and which differ markedly between different cities.

In 1959, an apparently new environmental factor was brought to the world's attention when an excess of the extremely rare tumor, malignant mesothelioma of the pleura and peritoneum, was found in persons living around crocidolite asbestos mines in the Cape Province of South Africa. While this was not the first demonstration of an adverse health effect on persons living near an industrial operation, it had worldwide implications because of the universal use of asbestos. In the laboratory, it was possible to demonstrate that all varieties of asbestos fiber, as well as other fibers of certain dimensions, could produce this tumor when injected intrapleurally or placed on the pleurae of experimental animals. The demonstration of exposure of the general population to fibers by counts of ferruginous bodies in the lung raised the question of whether fibers in community air posed a serious hazard for the general population. Shape and particle size of community particulate pollutants took on new significance as the potential for general population exposure to pollutants causing a specific, otherwise rare, disease was realized. This problem has been extensively studied in Canada, a major producer of one variety of asbestos, chrysotile.

The difficulty of demonstrating health effects related to particle exposures in the community was referred to earlier. In industries where persons have been exposed to high levels of certain particles for extended periods of time, adverse health effects have long been recognized. Here exists the opportunity to seek clues to the effects of particles on health and to identify the characteristics of particles important in producing such effects. The group of lung diseases known as the pneumoconioses (e.g. silicosis, asbestosis, and coal miners' pneumoconiosis) are examples of the long-term effects of exposure to certain particles. Over the last 20-30 years, it has also been accepted that certain particles, when inhaled, can result in increased risks of lung cancer for employees. Some particles have also been demonstrated to produce tumors at sites other than the lung (e.g. asbestos and gastrointestinal tumors, β-naphthylamine and bladder tumors). Nasal tumors have been shown to occur more frequently among workers exposed to certain types of wood dusts, and there are other examples of industrial diseases which appear to be related to specific types of particle exposure.

Exposure to particles which can be absorbed rapidly through the lungs into the bloodstream can lead to systemic poisoning (e.g. lead fume). In addition to long-term or chronic effects of exposure to particles, there are examples of acute reactions such as fume fevers (e.g. zinc) and morning reactions to exposure to dusts (e.g. cotton).

Industrial health problems are somewhat easier to identify and quantify, because exposures have been relatively high and have often been over long periods of time. As a result, much of what is known about the possible effect of particles of various sizes and shapes is derived from industrial experience. The interpretation of these observations in terms of health effects and hazards for the community has to take account of differences in the composition (age, sex, state of health) of the general population compared with that of industrial workers who represent a select segment of the population, as well as of differences in levels and complexities of community exposures. This presents serious difficulties.

An alternative approach to determining the role that particle size and shape play in producing health effects is to study the factors influencing the nature of particles to which the general population is exposed, and to investigate the mechanisms by which particles of specific sizes and shapes produce biological reactions at the cellular and other levels. This approach might provide clues to potential hazards and potential health effects. It is this second approach that is followed in this document, using existing literature and input from scientists in various parts of Canada in an attempt to answer the following questions:

- What is the present state of knowledge concerning the mechanisms and parameters which affect particle entry and deposition in the respiratory system?

- What are the mechanisms which effect particle removal from the respiratory system, and what are the sizes and shapes of particles which remain in the lung?

- Are particles transported from the lung to other organs of the body, and, if so, by what mechanisms?

- Do the size and shape of particles deposited in various parts of the respiratory system play any role in tissue reactions?

- What conclusions can be derived from industrial experience concerning the role of particle size and shape in producing health effects which might be relevant to elucidating the effects of air pollutants on community health?

- Is there any evidence from community health studies in Canada or elsewhere that particle size and shape are important?

- What is known about the size and shape of particles in community air in Canada?

- Can existing knowledge of particle size and shape be used to advantage in studying or controlling air pollution in Canada, and what research is in progress in this area in Canada?

- Does the present state of knowledge of particle size and shape permit the determination of the best approach to community health studies which is likely to fill gaps in knowledge successfully?

This report attempts to supply answers to at least some of these questions. It deals with the nature and size and shape characteristics of airborne particles; the deposition, clearance, and retention of inhaled particles in the respiratory system; the response of tissues to inhaled particles; and the human health effects of inhaled particles.

It should be emphasized that this report is concerned only with clarifying the role of particle size and shape in producing health effects, and does not address effects on animal life or vegetation, or other environmental impacts which might occur as a result of particulate air pollution. It also does not include secondary effects on humans resulting from exposure of animal life or vegetation to air pollution, effects which are certainly of importance but which merit separate study.

2.0 NATURE AND SIZE AND SHAPE CHARACTERISTICS OF AIRBORNE PARTICLES

2.1 NATURE OF AIRBORNE PARTICLES

The particles of interest in evaluating health effects are solids or liquid droplets suspended in air (collectively known as aerosols) which may be inhaled. Airborne particles may range in size from molecular dimensions up to about 100 μm in diameter. The main types of particles are dusts, mists, fumes, and smokes.

Airborne dusts consist of solid particles rendered airborne during crushing, grinding, or attrition of hard, rocklike materials, by dispersal of fine particles from bulk sources, and by reentrainment of previously deposited particles. Dusts are generally irregular in shape.

Mists are produced by spraying liquids or are formed by condensation from air saturated with vapor. Mists contain droplets which are spherical.

Fumes (usually metals), formed by condensation processes, are generally very small and can be irregular in shape (Roach 1973). Secondary fumes which are produced by dispersion into air of fumes from bulk sources or by redistribution of settled primary fume particles are invariably coarser in size than the fumes originally emitted.

Smokes are particles formed from combustion of organic matter. Typical dusts, fumes, mists, and smokes, with an indication of their size ranges, are shown in Figure 2-1.

2.2 SIZE AND SHAPE CHARACTERISTICS OF PARTICLES

2.2.1 APPROXIMATELY SPHERICAL PARTICLES

For spherical particles, size and shape are defined rigorously by measurement of their diameters. However, most airborne particles of practical interest are not spherical, and a variety of empirical factors have been proposed in order to define size and shape which might then be correlated with particle behavior in fluids (in this case, air). For spheroidal particles, shape factors related to such particle parameters as volume (Heywood 1962), surface area, projected area, or projected perimeter are often used. Results obtained by light or electron microscopy are generally described by the projected area diameter, which is the diameter of a circle of the same area as the particle (Fraser 1973). The relation of the projected area diameter to other particle properties has been discussed by Davies (1961, 1962, 1964), Robins (1954), and Cartwright (1962). The light scattering diameter, defined as the diameter of a sphere having the same optical properties and ability to scatter the same amount of light as the actual particle, is utilized by optical particle counters in estimating size (Heyder *et al.* 1974).

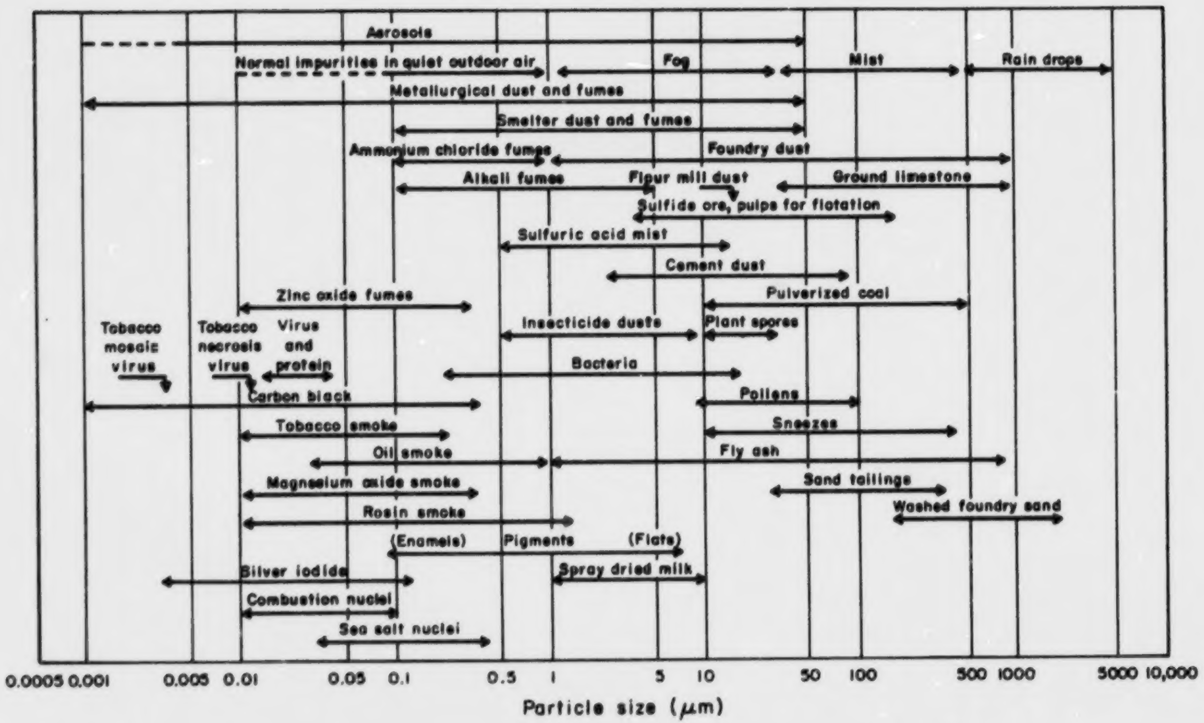

Figure 2-1. Approximate size ranges for airborne particles (from Stuart and Richland 1973).

2.2.2 HIGHLY NONSPHERICAL PARTICLES

When particles diverge markedly from spherical configurations, single length parameters and shape factors do not adequately describe the multiple characteristics of the particle.

Numerous characteristic diameters of nonspherical particles have been suggested in the literature. The various diameters which can be determined by observing the particle in an optical or electron microscope include the projected area diameter; Feret's statistical diameter, determined by the distance between parallel tangents for a number of particles (Feret 1931); and Martin's diameter, which is the mean of chord length of the projected outline of the particle (Martin et al. 1924; Timbrell 1965).

Some commonly encountered, highly nonspherical particles are talc, mica, vermiculite, asbestos, glass fibers, organic fibers such as cotton, and synthetic fibers. For such particles, two parameters are unlikely to reflect their aerodynamic behavior. At least three, and possibly four, parameters are needed to describe the sizes of plates and fibers.

Fiber shape is important in determining possible deposition of fibrous aerosols, such as asbestos, in the human respiratory system. Fibrous particles may be characterized by four of the following: (i) actual length; (ii) actual diameter; (iii) coil length; (iv) coil diameter; (v) aspect ratio, defined as the ratio of the actual fiber diameter and actual length of fiber; and (vi) coil aspect ratio, which is the ratio of the length to diameter of an imaginary cylinder enclosing a curly fiber (Timbrell 1970).

Cotton and certain other fibers, both naturally occurring and man-made, can be curly. The most striking physical difference between the two groups of asbestos minerals is their shape: the amphiboles are straight and the serpentine variety of chrysotile can be curly. In the case of a straight fiber, without adhering particles, the coil aspect ratio is equal to the aspect ratio.

It should be noted that these parameters give only a simplified description of fiber shape. Fibers are not all truly circular in cross section; for example, crocidolite asbestos fibers are elliptical.

Plates or flakes may be characterized by (i) length; (ii) width; (iii) ratio of length to width; and (iv) thickness. A further complication arises when considering plates which are not flat.

2.2.3 AGGLOMERATES AND AGGREGATES

An agglomerate consists of two or more particles which are held together by relatively weak cohesive forces (e.g. electrostatic).

An aggregate is a particle or assembly of particles held together by strong inter- or intramolecular or atomic cohesive forces. The study of the behavior of aggregates and agglomerates is more complex than that of single particles because of the difficulties of characterizing shape and density and of describing the form in which they exist in air. This is a serious problem in studying community air pollutants, because most particles do not exist singly and most collection methods disrupt their original form. Most asbestos fibers which are visible by optical methods are bundles, and particles can adhere to their surface resulting in a multiplicity of different shape characteristics.

2.2.4 AERODYNAMIC SIZE

It is important to note that in the literature, particularly in reports concerned with the biological activity of particles, the term "diameter" is often used improperly. Furthermore, definitions of aerodynamic diameter and other diameters are often confused.

In order to overcome some of the difficulties of working with individual airborne particle sizes, it is often more convenient to consider particles as equivalent if they exhibit the same aerodynamic behavior. The physical dimensions of a particle become exclusively important after the particle has been deposited in the lung.

In health studies where the hazards are related to, and expressed in terms of, the total mass of particles inhaled or deposited in the respiratory system, the equivalent volume diameter, defined as the diameter of a sphere having the same density and volume, becomes an important parameter.

Stoke's equivalent diameter and the aerodynamic diameter determine whether a particle will be deposited in the respiratory system and the location of such deposition (e.g. nasal passages, buccal cavity, tracheobronchial tree, or the alveoli; see Chapter 3). Stoke's diameter is the diameter of a sphere which has the same density and terminal settling velocity as the particle. Both Stoke's diameter and the density of the particle are required to define the particle's aerodynamic properties. The aerodynamic diameter is the diameter of a sphere of unit density which has the same terminal settling velocity as the particle. All particles of the same aerodynamic diameter, regardless of their shape or density, will have the same aerodynamic behavior when the force acting on them is related to their mass.

2.3 CHARACTERISTICS OF AEROSOLS

A monodispersed aerosol is one in which all particles are of the same size. It is impossible to obtain this in practice, and the majority of natural and man-made aerosols possess considerable polydispersion, necessitating the introduction of parameters describing the mean size and size distribution of particles. A knowledge of the particle size distribution is important in assessing the potential health hazard through inhalation and deposition in the respiratory system. However, more often than not, an indication of the mean particle size, instead of the size distribution, may be all that is available.

2.3.1 MEAN SIZE OF AEROSOL PARTICLES

The mean particle sizes measured and calculated in different ways may differ considerably from one another as a result of the dispersion of the airborne particles. Therefore, in investigating the effects of particles on health, it is important to gather preliminary data on the most likely physical parameter(s) of the particles responsible for the hazard, and, subsequently, to calculate the mean particle size based on that physical parameter. For example, there exist particulate contaminants for which the important parameter determining the toxicity and the degree of health hazard involved may be the surface area of the particle. For toxic chemicals with very low dissolution rates and airborne particulate matter with radioactive particles attached to its surface, the surface mean diameter, based on the surface area of the particle, would then be an appropriate parameter for assessing the size of the airborne particulate matter. The arithmetic mean diameter or the volumetric mean diameter would likely provide less accurate correlations.

Large and small particles receive equal representation when calculating mean particle sizes derived from distributions with respect to size. However, means derived from the distribution with respect to mass should be preferred in health studies where the total mass of inhaled particles may be the determining factor in assessing damage to the respiratory system. The geometric mean diameter, based on the logarithm of the particle diameter, is preferred when assessing the mean diameter of particles distributed lognormally.

Other methods of defining diameter which are frequently used in the literature are the number median diameter and the mass median diameter. The number median diameter is the diameter such that half the particles have larger diameters and half have smaller diameters. The mass median diameter is determined from the mass of the particles: the mass of particles with greater diameters is equal to half of the total mass of the aerosol.

Average sizes must be interpreted with caution, because the measurements of particle sizes in the distribution may be based on light optical observations only (hence, all sizes are not seen). In addition, measurements made using optical or automatic counters may observe different size fractions of the aerosol. The method of particle collection may also lead to disruption of the particles as they exist in air. This is seen in the case of impaction methods, which may break particle agglomerates into several particles of smaller sizes, and hence affect the reported particle size distributions.

2.3.2 PARTICLE SIZE DISTRIBUTION OF AEROSOLS

Due to the strong dependence of the physical properties of aerosols on particle size, a mean size is seldom sufficient to describe the behavior of a polydisperse system, and it is usually necessary to determine the particle size distribution.

The frequency distribution curve represents the fractions of the total number of particles having diameters in specific size ranges. Similarly, the weight distribution curve defines the weight fraction of particles with diameters between d and (d+dd). Alternatively, cumulative distribution curves show the fraction of particles (by number or weight) having diameters greater or less than a given value. The shapes of the particle size or mass distributions can vary. In very few aerosols, such as those formed by plant spores, the distribution curves are symmetrical and close to a normal distribution curve. However, it is often not a satisfactory representation of particle size distributions, since the distributions are often skewed, and the function always predicts finite probabilities for negative values of the variable. The lognormal distribution curve is more satisfactory than the normal distribution function for representing particle size distributions of most natural and man-made aerosols. When the number of particles in a given size range is distributed lognormally, the mass and other power functions of the radius are also distributed lognormally with the same standard deviation. The formation processes of both condensation and dispersion aerosols are complicated; therefore, the resulting distributions may be highly skewed, and it is common to utilize one of a series of empirical formulae developed in the literature (Rosin and Rammler 1933; Roller 1937; Nukiyama and Tanasawa 1938).

2.3.3 UNIMODAL, BIMODAL, AND TRIMODAL DISTRIBUTIONS

Community air is a mixture of particles from many sources. The particle distribution is complex, and the nature of particles in different parts of the distribution may be different. Due to the interaction of particles with one another, there is loss of certain sizes, and a preference shown for the formation of certain sizes of airborne particles. The result is that most aerosols in community air have bi- or trimodal distributions (Slinn 1975; Suck 1980; Lippmann 1980).

2.3.4 RELATIONSHIP BETWEEN SIZE AND SHAPE

For most types of spherical or nearly spherical particles, particle shape does not usually change with size. However, some types of particles, such as asbestos (fibers) or mica (platelets), may have one constant dimension which is not affected by particle size. For example, the diameter of the fibers of asbestos may be constant, while the fiber length and shape may change with increasing particle size. This imposes the problem of a changing shape and aspect ratio at different size ranges, and complicates attempts to define physically an aerosol containing such particles. Ideally, the size distributions of fibers should be given by length and diameter. This is not normally possible using optical methods. Until there are sufficient data concerning the dependence or nondependence of diameter on length for fibers, the description of one parameter is inadequate.

2.3.5 SIZE-SELECTIVE AIR SAMPLING AND RESPIRABLE FRACTIONS OF AIRBORNE PARTICLES

Throughout this text, we are concerned with the fraction of airborne particles which reach a particular site in the body where they can initiate a biological response. While the report does not deal with the measurement of airborne particle concentrations, sampling methods are important, and a few comments on particle sampling, size-selective samplers, and respirable fraction of airborne particles are warranted.

2.3.5.1 Measurement of Total Airborne Particle Concentrations and Size Distributions

While the collection of samples of airborne particles by drawing air through a filter, for example, would appear to be simple, the result can be influenced by sampler orientation and the linear entry velocity of air into the collector. When particles are carried in moving air, errors in the recorded mass and/or particle number are introduced unless the air enters the sampler at the same velocity as the velocity of the ambient air (i.e. isokinetically). Information on some of the errors has been reported by Sehmel (1967).

2.3.5.2 Respirable Fraction of Airborne Particles

As described in subsequent chapters of this report, the aerodynamic behavior of particles and their ability to enter the respiratory system are governed by shape, size, and density. Thus, it has been convenient to define those fractions of the airborne particles which enter various parts of the respiratory system, and methods have been devised to collect such fractions of airborne particles. A discussion of all the techniques and instruments available is beyond the scope of this report, but the criteria and two instruments deserve mention.

In 1959, the Johannesburg International Conference on pneumoconiosis adopted criteria proposed by the British Medical Research Council for defining "respirable fraction" in terms of the falling speed of particles. The Hexhlet horizontal elutriator was designed to provide a size cutoff compatible with the definition of respirable fraction (i.e. that fraction capable of penetration to the alveolar region). This fraction, $C/C_o = 1 - f/fc$, where C and C_o are the concentrations of particles with falling speed f of the respirable fraction and whole cloud, respectively, and fc is a constant equal to twice the falling speed in air of a sphere of unit density 5 µm in diameter. Other criteria such as those of the American Conference of Governmental Industrial Hygienists exist, and cyclones have been constructed and are utilized to conform to ACGIH criteria and to provide size cut-offs very similar to those of depositional curves for mouth breathing. However, cyclones are sensitive to design variables and operating conditions, rendering duplication and standardization of such an instrument difficult.

Another set of criteria was developed by the U.S. Atomic Energy Commission (AEC) in 1961 which defined a "respirable dust" in terms of the proportion of the inhaled dust which penetrates to the nonciliated portions of the lung.

Size-selective samplers have been designed and are utilized to measure "respirable" particle concentrations in particular industrial environments. It must be recognized that the "respirable fraction" measured by these various instruments may not be equally well defined. It must also be noted that those measuring deposition in the nonciliated portion of the lung only do not address the fractions of dust which might be rapidly absorbed (e.g. via the upper respiratory tract or gastrointestinal tract), or which may induce reactions higher in the respiratory tract. It should also be pointed out that such instruments are designed for size selection of spherical particles, and, while they can in some instances be used for nonspherical particle collection, shape factors can be important and attention must be given to defining exactly what the instrument collects. More detailed considerations of particle sampling can be found in Roach (1973), Lippmann (1976), and Atherley (1978).

3.0 DEPOSITION, CLEARANCE, AND RETENTION OF INHALED PARTICLES IN THE RESPIRATORY SYSTEM

Although airborne particles may occasionally enter the eye or be deposited on skin to produce irritation, those related to health effects enter the body almost exclusively through the nose and mouth by inhalation.

The ability of particles to initiate a biological reaction in the lung or produce systemic "poisonings" or "reactions" depends on: (i) their ability to enter the respiratory system (i.e. penetration); (ii) the site of deposition within the respiratory system; (iii) the extent to which they are retained; (iv) the rate of absorption of the particles and sites to which they are translocated; and (v) the biological activity of the particles, or their ability to carry biologically active agents into the respiratory system. Size and shape of particles play an important role in each of the above.

3.1 COMPARTMENTS OF THE RESPIRATORY SYSTEM

While the subdivision of the respiratory system into discrete segments is somewhat arbitrary, it is recognized that the probability of particles entering different parts of the respiratory system is governed by geometry and airflow patterns, in addition to particle parameters. At the same time, different removal mechanisms act at different levels within the respiratory system. Considerable attention has been given to the definition of the human respiratory system from the standpoint of understanding particle entry, deposition, and retention. One useful model is that proposed by the International Commission on Radiological Protection Task Group on Lung Dynamics (ICRP 1966), according to which the respiratory system is subdivided into three main parts: (i) the nasopharyngeal compartment; (ii) the tracheobronchial compartment; and (iii) the pulmonary compartment (Figure 3-1).

The nasopharyngeal compartment, comprising the nasal cavity and the nasopharynx, begins with the anterior nares and extends back and down, through the anterior and posterior pharynx, to the level of the epiglottis. The nose is the natural entrance to the respiratory tract and the first target for noxious environmental air contaminants, and it should be the first line of defence against them. The part of the nasal cavity immediately inside the nostrils (called the vestibule) is lined by skin bearing hairs; the remainder of the cavity is lined by mucous membrane. The total surface area of nasal mucosa approximates 160-180 cm^2, and the length of the nasal passages in an adult ranges from 8 to 11 cm. The smallest cross section of the nasal passages lies about 2 cm posterior to the nostrils and has a surface area of 20-40 mm^2 on each side. The linear velocity of inspired air at the level of the smallest cross section of the nose is normally 4.5-5.0 $m.s^{-1}$, and can be as high as 10-12 $m.s^{-1}$, compared with 2.0 $m.s^{-1}$ in the bronchial tree (Proctor and Swift 1971). Beyond this point, the velocity is reduced, but some turbulence develops as a result of changes of direction. Another bend

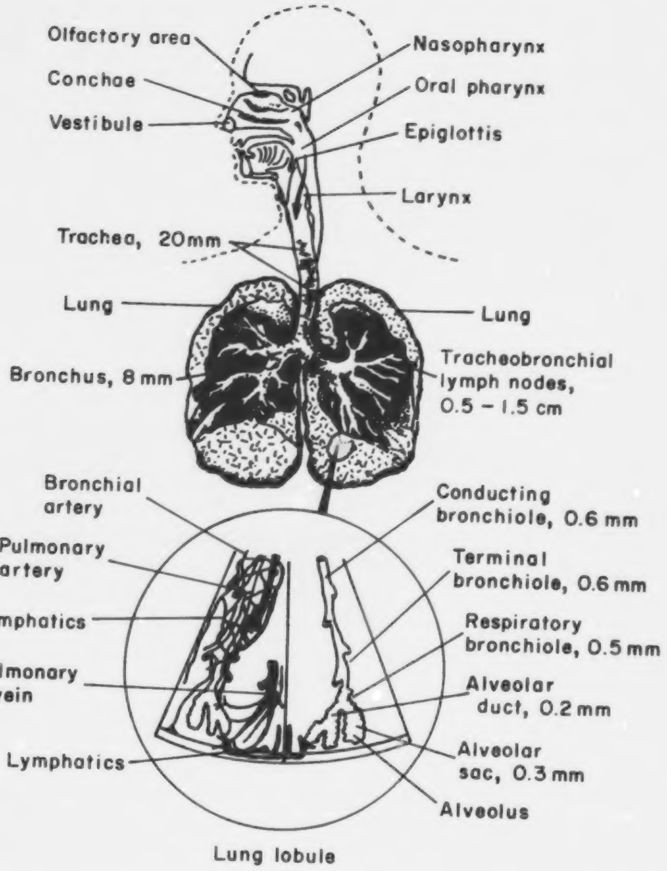

Figure 3-1. Schematic representation of the conducting airways in the human respiratory tract (from Stuart and Richland 1973).

occurs when the air passes from the nasopharynx into the oropharynx. This results in a very high deposition of inhaled particles at and just beyond the nasal entrance. During mouth breathing, deposition is high in the mouth and over the posterior pharynx.

The tracheobronchial compartment consists of the trachea and the bronchial tree down to and including the terminal bronchioles. The trachea and the bronchi are made up of 23 generations of dichotomous branching tubes. The nasopharyngeal and the tracheobronchial compartments may be considered to constitute the anatomically dead space of the respiratory system. These two compartments represent the epithelial area of the respiratory tract which is ciliated and covered with mucus arising from goblet cells and secretory glands.

The pulmonary compartment consists of respiratory bronchioles, alveolar ducts, atria, alveoli, and alveolar sacs. The surface of this compartment consists of nonciliated, moist epithelium, with none of the secretory elements found in the tracheobronchial tree. The pulmonary compartment may be regarded as the functional area of the lungs where exchange of oxygen and carbon dioxide between air and blood takes place. The number of alveoli has been estimated to be 300 million, together with 14 million alveolar ducts. The diameters of the alveoli range from approximately 150 to 400 μm, and it has been suggested that the total alveolar surface area varies between 30 and 80 m^2 (Mitchell and Tomashefski 1964).

3.2 MECHANISMS OF PARTICLE DEPOSITION

Deposition may be defined as the process determining the fraction of inspired particles caught in the respiratory tract. It is generally assumed that once a particle touches a surface it is deposited with no subsequent reentrainment, and, hence, the site of contact is also the site of initial deposition.

Three distinct physical mechanisms - inertial impaction, gravitational settling, and Brownian diffusion - operate on particles suspended in the inhaled air and cause particle trajectories to move across fluid streamlines towards the surface of the respiratory tract. For fibrous aerosols, an additional mechanism - interception - becomes important.

3.2.1 INERTIAL IMPACTION

The multiple branching in the airways of the respiratory system causes sudden and multiple changes in the direction of airflow. Because of their inertia, particles tend to continue in their original trajectory crossing fluid streamlines and eventually impact on the airway walls. The fraction of deposited particles is a function of the terminal settling velocity, the velocity of the airstream, the radius of the respiratory airway, and the bend angle of the airway radius.

Typically, impaction becomes important for particles with an aerodynamic diameter greater than 1 µm.

3.2.2 GRAVITATIONAL SETTLING

Every particle allowed to fall in air will accelerate under the force of gravity to a terminal settling velocity, such that the force of gravity is balanced by the drag on the particle caused by its movement through air. Typically, for particles of a few micrometres in diameter, this terminal velocity will be reached in a fraction of a second. The gravitational force is determined by the mass of the particle, which in turn depends upon its volume and airborne density. The resisting or drag force on the particle, on the other hand, is a complex function of the particle's size, density, shape, and the physical characteristics of the fluid, and is therefore not easily determinable. For very small particles with diameters of the same order of magnitude as the mean free path of the air molecules, air resistance decreases, and the Cunningham correction factor has to be used to account for a slip through the air molecules and to determine the drag force of the particle (Dahneke 1973). Gravitational settling is one of the primary mechanisms of deposition of inhaled particles with aerodynamic diameters larger than 0.1 µm.

3.2.3 BROWNIAN DIFFUSION

Because of Brownian movement, the trajectories of very small particles do not coincide with the streamlines of the gas, even in the absence of other effects. Particles will migrate to a surface and be deposited purely as a result of this random diffusional motion. As the Brownian movement of an airborne particle increases with decrease in particle size, diffusional collection increases. Brownian diffusion becomes increasingly important for particles less than 0.5 µm in diameter.

3.2.4 INTERCEPTION

Most studies of particle deposition in the respiratory system have assumed that the above three collection mechanisms are the only ones that need to be considered in order to estimate deposition. In determining deposition by inertial impaction, the particles are assumed to be point masses in the calculation of the deposition efficiency. Their size is accounted for in the evaluation of the fluid's resistance to the particle motion. Similarly, for gravitational and diffusional deposition, the particles are assumed to be infinitely small, and their size is accounted for when determining fluid drag or the distance from the surface of the collecting surface for collection deposition.

The above procedure, although relatively accurate and straightforward when dealing with spherical or spheroidal particles, is in error when the inhaled particles have a highly nonspherical shape, as with fibers, needles, plates, and others. For such particles, the deposition efficiency based on the aerodynamic or Stoke's diameter is not sufficient. The shape of the particle and its orientation in the streamline influence its interception and subsequent deposition. This mechanism is discussed in Section 3.4.2.

3.2.5 OTHER CONSIDERATIONS

There are other factors that must be considered when assessing the mechanisms determining particle deposition in the respiratory system. Because such deposition mechanisms as diffusion and sedimentation are interactive, they cannot be assumed to be additive (Wang et al. 1968). Evaporation or hygroscopic growth of particles during respiration means that particle size changes continuously, and exhaled particles may be a different size than when inhaled. The density of individual particles and aggregates will not be the same even if size and shape changes are considered.

Particles made airborne by grinding, aspiration, and combustion may be electrically charged, even though the net charge of the resultant aerosol may be zero. Charging of individual particles will result in increased aggregation, especially in the smaller size ranges, causing alterations in the particle size distribution. Charged fine particles will obtain higher mobilities, which may in turn cause increased deposition, especially in the nasopharynx.

Although it was claimed by Stuart and Richland (1973) that thermal forces are probably not important in determining particle deposition within the respiratory system, not much experimental work has been performed to measure the effect of thermophoresis, which may be important in cold climates where the temperature of the inhaled air is much different from body temperature. Furthermore, increased temperature will slightly increase the Brownian motion of particles, thus enhancing diffusional deposition (Morrow 1960). Takagi et al. (1967) reported that the action of cold air and carbon dioxide on nasal airflow resistance may influence particle deposition in the nasopharyngeal region.

Davies (1974) demonstrated that the rate-determining factor for deposition of certain particle sizes is not necessarily one of the particle collection mechanisms. There is practically no difference between the deposition of 0.5- and 1.0-µm particles during breathing, although their rates of sedimentation are 1×10^{-3} and 3.5×10^{-3} $cm.s^{-1}$, respectively. Selective sampling apparatus used in industry for the measurement of "respirable" dust is designed assuming gravitational settling is responsible for the deposition of particles of these sizes in the alveoli. Davies (1974) considered such an approach not completely valid, claiming that the factor determining the rate of particle deposition in the 0.5- to 1.5-µm size range is not sedimentation but the mechanical mixing of the tidal and reserve air in the dead space of the first two compartments of the respiratory system.

3.3 TOTAL AND REGIONAL DEPOSITION

Particle deposition in the respiratory system is a complex phenomenon; where particles come to rest is governed largely by the characteristics of the particles and the physical laws of particle deposition. Biological factors, including lung function, amount of work performed (and, hence, breathing rate), age, sex, and general physical condition, as well as anatomical variations between individuals, may also be important in assessing the likely outcome of exposure to airborne particles.

Numerous experimental studies using human and animal subjects have been conducted to measure total deposition within the respiratory system. Studies of regional deposition have been fewer in number, and have proved to be relatively more difficult to perform and to evaluate.

3.3.1 TOTAL DEPOSITION STUDIES

Total deposition studies were compiled by Stuart and Richland (1973), Davies (1974), and Stuart (1976). Stuart's compilation (Stuart and Richland 1973) is reproduced in Figure 3-2.

There is reasonable agreement between experimental total deposition studies. Deposition increases with increasing aerodynamic diameter for particles with aerodynamic diameters greater than about 0.5 µm. Approximately 90% of particles with 5-µm aerodynamic diameters and, as inferred from the graphs of Figure 3-2, essentially all particles with aerodynamic diameters greater than 10 µm either are deposited or do not enter the pulmonary compartment. Increased deposition with increasing particle size implies that the dominating deposition mechanisms are inertial impaction and gravitational settling. For particles with aerodynamic diameters smaller than 0.5 µm, deposition increases with decreasing size, implying that diffusional deposition is the main collection mechanism.

Although the same qualitative conclusions may be drawn from the data shown in both parts A and B of Figure 3-2, it is unlikely that the enormous scatter in results is wholly attributable to experimental error and to differences in shapes and densities of test aerosols. This implies that deposition in the respiratory system is more complex than has been previously realized. Physiological and biological parameters that may affect deposition are discussed in Section 3.5.

3.3.2 REGIONAL DEPOSITION STUDIES

Because different health effects arise in different parts of the respiratory system, and because clearance mechanisms vary with

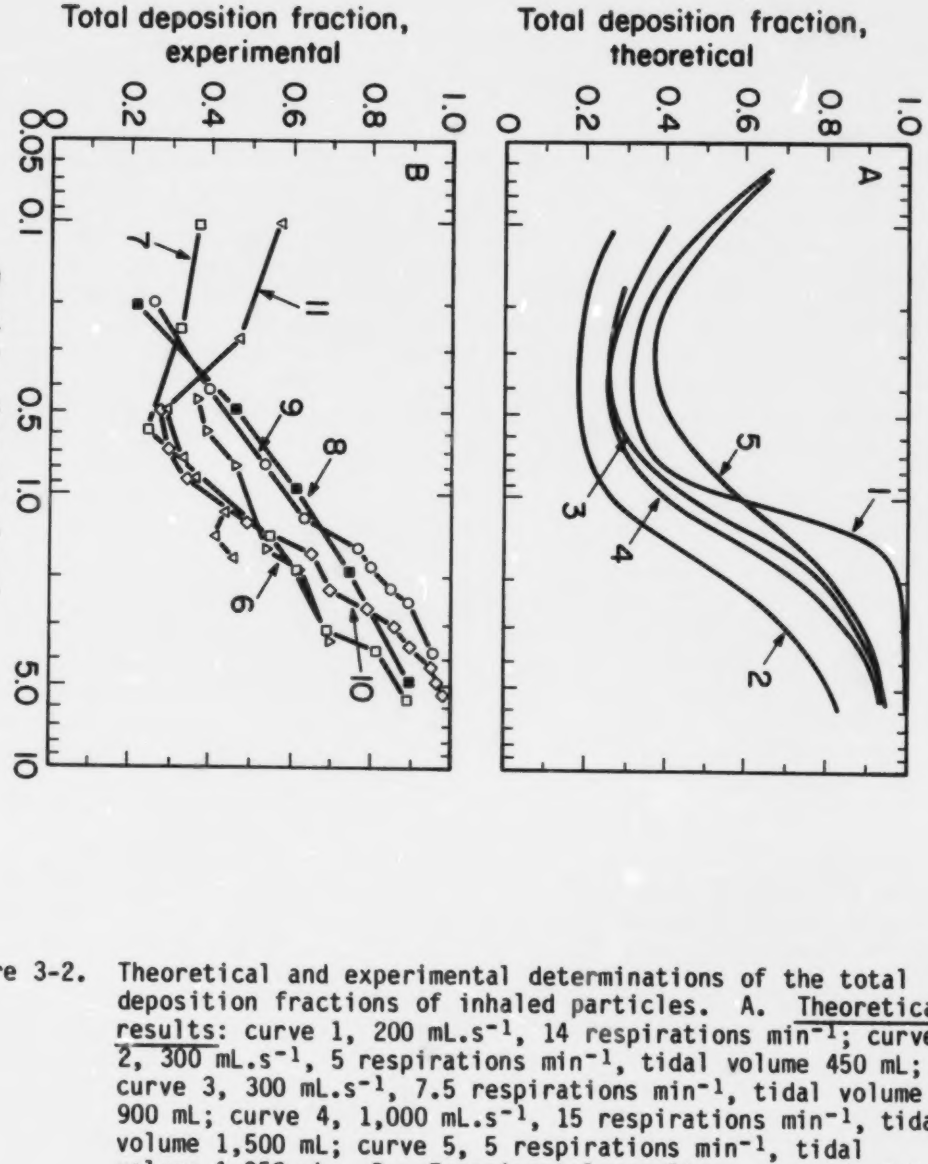

Figure 3-2. Theoretical and experimental determinations of the total deposition fractions of inhaled particles. A. Theoretical results: curve 1, 200 mL.s^{-1}, 14 respirations min^{-1}; curve 2, 300 mL.s^{-1}, 5 respirations min^{-1}, tidal volume 450 mL; curve 3, 300 mL.s^{-1}, 7.5 respirations min^{-1}, tidal volume 900 mL; curve 4, 1,000 mL.s^{-1}, 15 respirations min^{-1}, tidal volume 1,500 mL; curve 5, 5 respirations min^{-1}, tidal volume 1,350 mL. B. Experimental results: curve 6, 5.5 respirations min^{-1}; curve 7, 7.5 respirations min^{-1}, tidal volume 900 mL; curve 8, 15 respirations min^{-1}, tidal volume 700 mL; curve 9, 19 respirations min^{-1}, tidal volume 700 mL; curve 10, 13.3 respirations min^{-1}, tidal volume 720 mL; curve 11, 10 respirations min^{-1}, tidal volume 990 mL (from Stuart and Richland 1973).

location, it is necessary to know the characteristics of the particles which may enter and be deposited in different parts of the respiratory system.

3.3.2.1 Nasopharyngeal Compartment

Particle deposition in the nasopharyngeal compartment was investigated by Landahl and Tracewell (1949), who passed aerosols of sodium and potassium bicarbonate, glycerol mists, corn oil, and methylene blue through the nose and mouth of experimental subjects. These investigators were the first to confirm experimentally that the largest particles (>10 μm) would be preferentially removed from the aerosol in the nasopharyngeal compartment, and that the predominant collection mechanism for these large particles was inertial impaction.

Nasopharyngeal deposition of several sizes of monodispersed methylene blue particles produced by a spinning disc generator was studied by Pattle (1961), who correlated his experimental results in the form of a semiempirical equation relating nasal deposition (ND) for particles with aerodynamic diameter, d_A (μm), to the square of the diameter and to the volumetric flow rate, $\dot{V}$ ($L.min^{-1}$):

$$ND = -0.62 + 0.475 \log d_A{}^2 V \qquad (3\text{-}1)$$

This curve predicts that particles of the largest inhalable size (>20 μm) will deposit almost exclusively in the nasopharyngeal compartment. The ICRP Task Group on Lung Dynamics (ICRP 1966) adopted Pattle's correlation as a basis for their calculations of deposition in the nasopharyngeal compartment. This was criticized by Mercer (1975), who claimed that deposition in the tracheobronchial compartment was underestimated.

Hounam (1971) improved on the state of the art with experiments on the deposition of radioactive monodispersed polystyrene particles, ranging in diameter from 1 to 10 μm, inhaled through the nose and mouth at flow rates in the range of 5-37 $L.min^{-1}$. His experiments permitted the pressure difference across the nose and mouth to be determined as deposition occurred. When deposition was plotted against flow rate for particles of the same size, there was considerable scatter in the results. A better correlation was found when deposition was examined in relation to the pressure difference. Hounam's (1971) results are summarized by the following equation:

$$ND = -0.975 + 0.66 \log d_A{}^2 \Delta P \qquad (3\text{-}2)$$

where ΔP represents the differential pressure between mouth and nose in millimetres of water pressure. Correlating deposition with pressure drop may be more advantageous, because pressure drop is an indicator of the inhaled air turbulence, and reflects the interaction of the anatomical cross section with airflow.

The deposition of submicrometre particles in the nasopharyngeal compartment has also been studied by Hounam (1971). In a comparison of his experimental results with theory, he obtained good agreement if he assumed that atmospheric condensation nuclei behaved as if they were 0.01 μm in diameter. In experiments with iodine vapor, he determined that nasopharyngeal deposition increased with decreasing flow rate, indicating a diffusion-controlled deposition mechanism. Local deposition in the nasopharyngeal compartment was studied by Lippmann (1970), who found that 30-65% of a monodispersed aerosol with aerodynamic diameter between 1.1 and 4.6 μm was deposited in the non-ciliated anterior nares. Fry and Black (1973) measured a 45% deposition in the anterior portions of the nasal airways for 2- to 10-μm particles.

Particles trapped in the nose may be removed by blowing the nose or by nasal irrigation, or may pass to the mouth and be swallowed, thus entering the gastrointestinal tract. Those particles that remain in the nasal passages can, in some circumstances, give rise to certain diseases. For example, an increased risk of nasal tumors has been demonstrated among leather workers in the boot and shoe industry (Acheson et al. 1970) and among woodworkers (Acheson et al. 1972). Particles deposited in the nose may also be responsible for the perforation of the nasal septum described among potash miners (Williams 1974).

Particles which pass through the nasal passages or are inhaled through the mouth may, depending on size, shape, and density, be impacted in the upper respiratory tract, be deposited on or near the mucociliary escalator and moved upwards by cilia and swallowed, or be deposited deep in the lung.

3.3.2.2 Tracheobronchial Compartment

Experiments on particle deposition in the tracheobronchial compartment of the respiratory system have usually involved inhalation through the mouth, which bypasses most of the nasopharyngeal compartment. Lippmann and Albert (1969) extensively studied the effect of particle size on the regional deposition of aerosols through the mouth using 34 male and female subjects, smokers and nonsmokers. The test aerosols were spherical monodispersed insoluble iron oxide particles containing radioactive tags. The median diameters of the aerosol particles varied from 1.3 to 7.9 μm and the geometric standard deviation averaged 1.08. Deposition was measured by head monitoring and external lung measurements with the use of scintillation detectors. While deposition in the mouth did not vary significantly from subject to subject, the pharynx plus larynx region showed marked intersubject variation in particle deposition. The authors showed that inertial impaction was the dominant mechanism for tracheobronchial deposition, at least for particles larger than 4-μm unit density spheres. Calculated deposition fractions for the larger particles indicated that most of the deposition should occur within the first four generations, and that the deposition in the tracheobronchial tree beyond the twelfth generation should be due to sedimentation.

Particle deposition in the tracheobronchial tree was studied by Schlesinger and Lippmann (1972) by means of hollow Silastic casts extending from the trachea through the segmental bronchi. A tagged, monodispersed test aerosol was drawn at a constant inspiratory flow rate through the casts. The results indicated that deposition was low for particles with aerodynamic diameters below 3.5 µm, but increased rapidly with increasing diameter between 3.5 and 12.2 µm. Most of the impaction occurred at the bifurcations. Deposition increased with depth down to the segmental bronchi. At the tracheal bifurcation, the authors detected the greatest particle accumulation along the carina, and related the reported distribution of sites of bronchial carcinoma to the distribution of observed impaction sites.

Proetz (1951) introduced cigarette smoke and chemical powders into casts of the upper respiratory tract in order to study particle deposition in normal and obstructed air passages. His results agree with those of Schlesinger and Lippmann (1972) in that he observed increased particle deposition immediately distal to any bend or constriction in the airway.

Chan and Lippmann (1980) studied the regional deposition of inhaled particles (0.2-7 µm in diameter) in nonsmoking human volunteers. They described a new anatomic parameter, the bronchial deposition size, which represents an overall bronchial constriction index, and which allows individuals to be classified according to the fraction of inhaled particles which deposits within their tracheobronchial compartments. The average value obtained for 26 healthy nonsmokers was 1.20 cm, as compared with 1.02 cm for 46 cigarette smokers, 0.90 cm for 19 patients with obstructive lung disease, and 0.60 cm for 6 severely disabled patients.

3.3.2.3 Pulmonary Compartment

The pulmonary compartment differs from the nasopharyngeal and tracheobronchial compartments in that it constitutes the functional area of the lungs where exchange of oxygen and carbon dioxide between air and blood takes place. As such, it is perhaps the most important and sensitive part of the respiratory system.

Pulmonary deposition of inhaled particles in this compartment has been studied experimentally by Wilson and La Mer (1948), who measured the total and alveolar deposition of radioactively labelled, monodispersed glycerol and water aerosols at breathing rates of 5-20 cycles per minute. Brown *et al.* (1950) studied regional deposition, during nose breathing, of monodispersed aerosols of china clay at constant minute volume and different breathing rates. In their experiments, the exhaled air was collected in seven sequential compartments, and the carbon dioxide content of each fraction was used as a tracer to identify the region from which the air originated. Altshuler et al. (1967) criticized the validity of these data on the grounds that the diffusivity of carbon dioxide is much larger than that of inhaled particles.

Altshuler et al. (1967) studied alveolar deposition using three subjects, breathing through the mouth, and concluded that maximum alveolar deposition takes place for particles having an aerodynamic diameter larger than 2 μm. Stahlhofen et al. (1980) studied regional deposition of aerosol particles in the respiratory tract of normal nonsmokers, finding that maximum alveolar deposition occurs for particles with aerodynamic diameters between 3 and 4 μm, and that alveolar deposition decreases rapidly with increasing aerodynamic diameter above about 4.5 μm. In contrast, Davies (1972) studied the size distribution of particles deposited in the lungs and concluded that particles deposited preferentially in the lung have diameters less than 1.5 μm. Gessner et al. (1949) studied the pulmonary deposition of inhaled silica dust and observed decreasing alveolar deposition of particles with diameters larger than 1 μm.

Theoretical and experimental results of pulmonary deposition studies are summarized in Figure 3-3. It appears that for particles with diameters in the range of 0.2-5 μm, deposition in the pulmonary compartment of the respiratory system varies from 20 to 60%, with a maximum deposition for particles with 1.2-μm aerodynamic diameter.

As particle diameter decreases, the importance of diffusional deposition as a dominant collection mechanism increases. Based on theoretical and experimental data, Morrow (1973) estimated a second maximum of 80% to occur around a diameter of 7 nm. Stauffer (1974) calculated that newly formed H_2O-H_2SO_4 aerosols produced by "heteromolecular" nucleation and condensation from water and sulfuric acid had diameters between 2 and 20 nm. He theorized that, as a function of relative humidity, droplets smaller than 7 nm would have a probability of growing hygroscopically inside the pulmonary region. He concluded that the hygroscopic growth of such droplets to 7 nm is not important for measurements of the deposition maximum. However, for particles in the size range of 40-600 nm, hygroscopic growth will alter the regional deposition as calculated by the Task Group model (Ferron 1977).

3.4 DEPOSITION STUDIES WITH FIBROUS PARTICLES

A fiber, from the standpoint of evaluating health risks, is considered to be an elongated particle with a length:breadth ratio (aspect ratio) of at least 3:1 (British Occupational Health Society 1968; Edwards and Lynch 1968). As pointed out by Rohl et al. (1977), this definition is somewhat arbitrary and is currently the subject of controversy, because many technically nonfibrous particles might be counted as fibers.

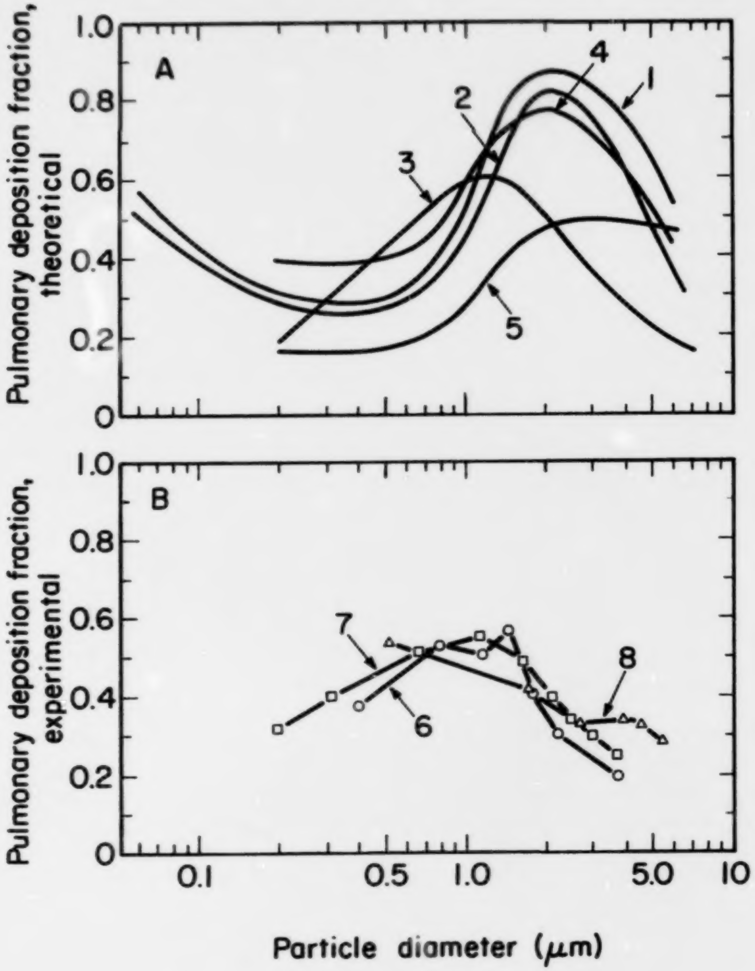

Figure 3-3. Theoretical and experimental determinations of pulmonary deposition fractions of inhaled particles. A. Theoretical results: curve 1, 14 respirations min^{-1}, deposition in respiratory bronchioles and below; curve 2, 14 respirations min^{-1}, deposition in alveolar ducts and sacs; curve 4, 300 mL.s^{-1}, 5 respirations min^{-1}, tidal volume 1,350 mL, deposition in bronchiole and smaller airway; curve 5, 15 respirations min^{-1}, tidal volume 450 mL, deposition in respiratory bronchioles and below. B. Experimental results: curve 6, 5.5 respirations min^{-1}; curve 7, 15 respirations min^{-1}, tidal volume 700 mL (from Stuart and Richland 1973).

With the exception of data on asbestos and glass fibers, the literature concerning the aerodynamic properties and deposition of particles which deviate widely from sphericity (e.g. mica plates) is sparse.

In view of the known hazards of asbestos and unknown risks of exposure to other fibers, there have been no experimental studies on humans to determine total or regional deposition of fibers. An interesting approach to solving this problem is that developed by Cohen (1973), who found that magnetic chest scans can be used to indicate the regional deposition of magnetite dust in the lung. Measurements on Quebec chrysotile miners and millers showed that some workers have readily detectable quantities of magnetite in the lung, probably derived from the magnetite particles which adhere to the chrysotile fiber (Cohen 1973, 1978; Cohen et al. 1981). In order to interpret such chest scans, the relationships between airborne respirable asbestos fibers and magnetite particles are currently under investigation (Djamgouz 1982). If reasonable relationships are found, this method could provide a means of indirectly inferring fiber deposition in the lungs of a working population. Such a technique has been used in the determination of lung retention and clearance in arc welders (Kalliomaki et al. 1978), in coal miners (Freedman et al. 1979), and in foundry workers (Kalliomaki et al. 1979). On the other hand, interpretation of certain of the results of magneto pneumographic observations has been questioned by Sterling (1981) who expressed the view that additional information is needed on the interactions which take place between the particles in the lung and magnetic fields before widespread use is made of this technique.

Evans et al. (1973) and Morgan et al. (1975) conducted experimental studies of deposition in the respiratory tract of rats using radioactively labelled asbestos minerals. By exposing animals to standard reference samples of crocidolite, Evans et al. (1973) found that 50 ± 5% by weight of the deposited asbestos in rats was accumulated in the lower respiratory tract. Morgan et al. (1975) exposed male albino rats for 30 min to three different mass concentrations of radioactively tagged UICC[α] samples of chrysotile, amosite, crocidolite, anthophyllite, and a synthetic fluoramphibole. They found a slightly lower deposition for chrysotile at the end of exposure, with similar quantities of dust in the nasal tract, esophageal and gastrointestinal (GI) tracts, and lower respiratory tract for amosite, crocidolite, and chrysotile. Anthophyllite and the fluoramphibole penetrated less deeply. Although these studies have been useful in examining regions of

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[α] A series of standard reference samples of asbestos (amosite, chrysotile, anthophyllite, and crocidolite) were prepared by the International Union Against Cancer (UICC) for use in international studies of the effects of asbestos (Rendall 1970; Timbrell 1970).

deposition, the sensitivity of the methods is far below that of methods using electron microscopic examination of the tissues.

3.4.1 RESPIRABILITY OF FIBERS

Although it has long been recognized that long-term exposure to high concentrations of the fibrous hydrated silicates known as asbestos produces health effects in workers, there was little, if any, systematic attempt prior to 1964 to understand the aerodynamic behavior of fibers as it relates to health effects. This was not for lack of evidence that size was important, as several studies had indicated that fibrogenicity was probably related to fiber length (Vorwald et al. 1951; Wagner 1963).

Timbrell (1965) described a series of experiments which led to our present understanding of the factors influencing the ability of fibers to enter the respiratory system. By passing mixtures of airborne spheres of density 1.1 $g.cm^{-3}$, fibrous glass, and asbestos fibers (amosite, crocidolite, and chrysotile) through an aerosol spectrometer, he was able to demonstrate the equivalent settling rates of spheres and fibers of various dimensions. The results showed that the settling rate of a fiber was mainly dependent on the square of its actual fiber diameter, with length being of secondary importance only. By examining the angles of the fibers of aspect ratios less than and greater than 5:1 to the airstream in the spectrometer, Timbrell found no evidence of alignment at low aspect ratios. However, those fibers with high aspect ratios showed some tendency to align. The importance of these findings lies in the fact that the deposition of particles in the lung airways is related to the aerodynamic diameter.

Most particles with falling speeds greater than that of a 10-μm unit density sphere are deposited in the upper respiratory system by gravitational settling or by impaction. Unfortunately, the experiments by Timbrell (1965) included only a limited number of asbestos fibers of diameters sufficiently large to examine those fibers having the same settling rates as spheres of 10-μm diameter. This may be due to the difficulties in generating and keeping such asbestos fibers airborne. The results based on the few plotted points suggest that the diameters of amosite, crocidolite, and chrysotile fibers having the same settling rates as a 10-μm sphere of density 1.1 $g.cm^{-3}$ would be 3.4, 3.2, and 4.5 μm, respectively. Timbrell concluded in a later report (Timbrell 1973) that for the asbestos minerals, a fiber with a diameter of 3 μm would have approximately the same falling speed as a 10-μm unit density sphere, and the penetration of fiber bundles of partially opened and aggregate fibers greater than 3.0 μm in diameter into the aerosol spectrometer (and lung) is related to apparent lower falling speeds for their size.

While these data provided for a major advance in the understanding of fiber aerodynamic behavior, they have certain limitations which should be recognized. First, the fibers were examined by light microscopy, and fibers of considerable length can have diameters so fine as to render them invisible on the conventional light optical microscope. Second, in order to generalize the results to include other fibers, it is necessary to know the density of airborne fibers which may not be the same as bulk densities. Third, the entry velocity and hence the alignment of fibers may not be the same for inhalation as in the experiment using an aerosol spectrometer. Fourth, in practical situations, other particles adhering to the fibers may influence their aerodynamic behavior. Fifth, the 3-μm diameter as maximum for respirability refers to alveolar penetration; for other higher sites, fibers of greater diameter might penetrate. Also, 3 μm refers to asbestos fibers; fibers of lower density will have a higher diameter cutoff. This is important because the 3 μm has often been used erroneously to conclude that asbestos fiber substitutes which have different densities are not hazardous because they would not penetrate into the respiratory system.

The experiments described above are basic to an understanding of one of the factors influencing the entry and deposition of fibers in different parts of the respiratory system. Although there are problems with the analysis of fibers in tissues, the observations by Gross et al. (1970) that 70-99% (mean 85%) of fibers detected in lungs of city dwellers were less than 3 μm in diameter support the physical experimental studies. The presence of fibers over 50 μm in length in lung tissue also supports the experimental evidence (Beattie and Knox 1961; Gross et al. 1970).

Studies in the Quebec asbestos mines and mills showed that the presence of airborne fiber bundles with diameters greater than 3 μm is rare (Gibbs 1971). Based on diameter criteria alone, it is reasonable to assume that virtually all airborne asbestos fibers encountered in ambient air will be capable of penetrating to the alveolar region of the lung.

3.4.2 EFFECT OF FIBER SHAPE ON DEPOSITION

The entry and penetration of fibers to the alveolar region of the respiratory system are dependent not only upon the diameter of the fiber, but also on other factors.

For approximately spherical particles with diameters less than 10 μm, interception in the pulmonary airways is of little importance because the size of the particle is small compared with the airway diameters. Long thin fibers may not be deposited by gravitational settling in the upper respiratory tract, but when they reach the pulmonary air spaces (air sacs and alveolar region), interception becomes a major deposition mechanism because of the fiber length. Timbrell (1965) calculated the interception effect for nasal hair spacing of 100 μm and for a bronchial opening of 200 μm, with first generation branching to 14 μm followed by 4 and 8 branches. He concluded that the efficiency of interception was dependent on increasing fiber length and decreasing airway size. For example, a fiber 50 μm in length had a 50% probability of penetrating beyond 8 branches, and a fiber 100 μm in length had a 10% probability of penetrating beyond 8 branches. Fibers greater than 200 μm in length would not pass through nasal passages.

Although glass fibers and amphibole asbestos fibers tend to be straight, not all fibers are. Chrysotile, the most widely used variety of asbestos, can be curly. Wagner (1963) found the weights of dust in the lungs of rats exposed to equal mass concentrations of respirable chrysotile and amphibole (as defined by a horizontal elutriator) to differ considerably, with six times as much amphibole as chrysotile retained several months after exposure. Timbrell (1970) considered that this discrepancy could be explained in large part by the difference in lower penetration of chrysotile due to its curliness. This conclusion may not have been totally valid because elimination, differential solubility of the fibers, and other factors may also have reduced the quantity of chrysotile found in the lung. However, subsequent experiments with rats showed that, for the same number concentration, the mass of amphibole in the lung immediately after nose inhalation was 27 times that of chrysotile. This difference was considered to be due to the curliness of the chrysotile fiber and the relative difference in fiber diameters of the airborne fibers generated (Davies 1970). An experiment in which airborne UICC chrysotile (which contains a high proportion of curly fibers) was drawn through 100 tubes (1 cm long, 400 μm internal diameter) showed that there was a decrease in the penetration of fibers with increasing coil length or coil aspect ratio. This was in agreement with a consideration of interception effects in particle deposition mechanisms (Timbrell 1970).

Timbrell and Skidmore (1971) reported on the exposure of 6 SPF rats to 180 $mg.m^{-3}$, 8 $h.d^{-1}$, for 10 d to airborne glass fibers treated in a furnace to produce an aerosol containing straight fibers, curved fibers, and aggregates, together with spheres for comparison. The particles were produced by cutting strands of glass with a nominal diameter range of 0.75-1.5 μm using a microtome. The dust cloud contained fibers with a wide distribution of length, up to about 100 μm, and their actual diameter ranged from 0.8 to 9.4 μm. The size distribution of the various types of airborne particles and particle deposition in the whole lung were examined by optical microscopy. The results showed that fiber length was a major factor in the retention of fibers in rat lungs, but there was no clear difference between the rates of retention of straight fibers, curved fibers, and fiber aggregates. This was probably due to the dominant effect of fiber length which masked the effect of fiber shape and secondary dimensions.

Although airborne fibers encountered in industry are not as curly as those observed for UICC standard reference samples used in many of these experiments, length, diameter, and shape are all important in determining the lung burden. Hence the results obtained by the injection of fibers into the lung or into the pleura in animal experiments must be interpreted with great caution. Studies by Gibbs and Hwang (1975, 1980) showed that the mass of airborne fibers for the same number concentrations of the various asbestos types encountered in industry can be quite different because of the different fiber diameter-length distributions. The determination of whether various health effects are related to fiber number or to fiber mass is of great importance.

3.4.3 EVIDENCE OF FIBER DEPOSITION FROM TISSUE STUDIES

Examinations of the lung to determine which fibers are present, and hence to infer those characteristics which influence penetration, have also been carried out. This approach is useful, but results must be interpreted with care. Once fibers are deposited in the lung, they may be coated with iron protein to form ferruginous bodies, they may curl into balls, be removed, or moved to another location within the lung or body, or bundles may open to form many fibers or single fibrils. These processes may modify the quantity of fiber found and the fiber diameter-length distribution reported. Nevertheless, some very interesting observations have been made. Electron microscopic studies of lung sections from rats exposed to airborne dust clouds of UICC standard reference samples of asbestos (amosite, crocidolite, anthophyllite, and Canadian chrysotile) showed fibers of considerable length (>50 μm) to be present, with the longest fibers being located in the respiratory bronchioles and alveolar ducts, and distinctly shorter fibers being found in the lung tissue. The terminal air sacs contained a higher proportion of very short fibers than did the air ducts, which in turn contained a larger proportion of short fibers than did the dust cloud. The diameter distributions of amosite, crocidolite, and anthophyllite fibers in lung tissue of rats, in human lung tissue sections with pure asbestos exposures, and in the UICC samples were very similar, and decreased from anthophyllite through amosite to crocidolite (Timbrell et al. 1970). Studies of airborne crocidolite and amosite in South African mines and mills and manufacturing plants confirmed that actual airborne dust clouds contain amosite fibers with diameters distinctly greater than those of crocidolite fibers, and that the diameters of crocidolite change little in mineral processing. This suggests that the diameter distributions of these airborne amphibole fibers are very likely to reflect what enters and what is deposited in the lung (Gibbs and Hwang 1975, 1980).

3.5 PHYSIOLOGICAL PARAMETERS AFFECTING PARTICLE DEPOSITION

The deposition of airborne particles in the respiratory system is influenced not only by particle size and shape but also by physiological parameters. Brown (1931a,b) measured the effect of varying respiratory frequency, tidal volume, and minute volume on the deposition of particles using subjects breathing at rest, breathing under various work loads on a bicycle ergometer, and breathing air containing added carbon dioxide. He concluded that the percentage of particles deposited was inversely proportional to the respiratory rate, for rates below 20 min^{-1}, and to the minute volume. Deposition was not a function of tidal volume, vital capacity, relative humidity, or breathing rate for rates above 30 min^{-1}. Altshuler et al. (1967) found that slower, deeper breathing gave greater deposition than faster shallow breathing, and that this difference was more marked for larger particles (1.6 µm) than for smaller ones (0.14 µm).

Dennis (1961, 1971) pointed to an interesting phenomenon of minimum particle deposition at normal breathing frequencies of 15-20 min^{-1} and increased deposition when breathing rates were either higher or lower. In experiments using stearic acid particles, the breathing rates varied from 5 to 35 min^{-1} and the particle diameters studied were between 1 and 5 µm. Working with much smaller particles (0.04 µm, sodium chloride) and using both human subjects and dogs, Morrow and Gibb (1968) measured a decrease in the deposited fraction with an increase in breathing frequency. Contrary to Brown's (1931a) conclusion, an increase in tidal volume increased the deposition. These contradictory experimental results can be explained by considering the physical mechanisms responsible for deposition. For dominance of the inertial collection mechanism, deposition should increase with increasing breathing rate, while for gravitational settling and diffusional deposition, the reverse should be true.

It appears that the health of a subject is an important parameter affecting deposition. Lippmann et al. (1971), using test particles with 1.5-µm diameters, found that deposition in the tracheobronchial compartment was greatly enhanced in asthmatic and bronchitic patients, and was also higher than normal in cigarette smokers. Chan and Lippmann (1980) found similar results (see Section 3.3.2.2). Thompson and Pavia (1974a), using 5-µm diameter polystyrene particles tagged radioactively, performed experiments with healthy aged subjects and subjects with chronic bronchitis, and reported a deeper penetration into the healthy than into the bronchitic lung. Subsequently they claimed that their tests underestimated the difference in deposition between healthy and bronchitic lungs because the subjects were aged.

The penetration and subsequent deposition of airborne particles in diseased and obstructed lungs have not yet been fully investigated. Thompson and Pavia (1974a) and Pavia et al. (1977) discussed some factors contributing to the major differences in penetration between healthy persons and those with airway obstructive disease. As even minimum abnormalities in the airways are capable of prolonging the degree of turbulence of inhaled air, they result in an increased deposition in central areas relative to peripheral airways and alveoli. Pulmonary fibrosis, found in most pneumoconioses, tends to increase airway caliber and results in more ready access of dust to the deeper parts of the lung. Bronchitis, sometimes associated with pneumoconiosis, may play a protective role by limiting the entry of particles to the alveoli, and may account for the very slow rate of progression of simple coal workers' pneumoconiosis (Thompson and Pavia

1974b). The inverse relationship between bronchitis and coal workers pneumoconiosis was first pointed out by Gough (1960), who felt it was due to the dust particles being swept out of the lung by excess mucus.

The relationship between simple pneumoconiosis and particle deposition was investigated by Love et al. (1971) who, by experiments on the deposition of particles of 1-μm diameter in the lungs of two groups of coal workers with and without pneumoconiosis, concluded that there was little or no difference in the amount of aerosol deposited at a given tidal volume for the two groups.

There is some evidence that age may influence penetration and deposition in the respiratory system (Pavia and Thompson 1970; Milne and Williamson 1972; Palmes 1972; Stupfel and Mordelet-Dambrine 1974). Young children have, on the average, smaller airways which, by increasing the Reynolds number and pressure drop, should increase the efficiency of deposition. A higher metabolic rate than that of adults is likely to increase respiratory exchange and enhance penetration and deposition.

Although it is thought that sex may have an influence on biological reactions to inhaled toxic chemicals and particles, there is no evidence to support that sex affects possible deposition per se (Stupfel and Mordelet-Dambrine 1974).

3.6 CLEARANCE OF INHALED PARTICLES

3.6.1 CLEARANCE MECHANISMS

The term "retention" has often been used synonymously with "total deposition." This use is incorrect, as the quantity of particles retained in the lung at any point in time is equal to the amount deposited minus the amount removed by various clearance mechanisms. The time that particles remain in the lung is dependent on particle size and shape, site of deposition, particle chemistry, mineralogy, solubility, removal mechanisms, and other variables.

It is generally accepted that there are two clearance phases - rapid and long-term - based on the rate of removal of particles from the lung. Many of the particles which are deposited in the respiratory system are removed within the first few hours after deposition, while some remain for many years. The rate of particle removal from the lung is measured as a biological half-time. While it is possible to determine this half-time for such particles as soluble salts, which are rapidly absorbed from the lung surface, the biological half-times for relatively insoluble particles are generally not well known. The rapid phase of clearance has been well studied experimentally using radioactively tagged aerosols. In addition, techniques have been developed which might offer the possibility of studying longer-term clearance in people exposed to magnetic particles (Cohen 1978).

Relative to other factors, the importance of removal of trapped particles from the respiratory system depends on the rate at which the material elicits a physiological and/or pathological response. The biological effect of inhaling an irritant substance which produces a rapid response may depend more on the quantity of the substance deposited initially than on the rate of clearance. For example, the clearance rate for the inert dust, TiO_2, is slower than the clearance rate of the cytotoxic dust, silica (LeBouffant et al. 1974).

On the other hand, it is hypothesized that materials such as carcinogens, which may produce harmful effects only after long periods of exposure and after a long latent interval, exhibit activity only if the relative rates of clearance and deposition are such that a sufficient concentration of material remains in the body long enough to cause pathological damage. In such a case, the quantity of material deposited in the lung initially is likely to be of relatively minor importance, assuming that the initial dose is not sufficiently high as to impede the clearance mechanisms. Different clearance mechanisms operate in the different regions of the respiratory tract, so that the rate of clearance of a particle will depend not only on its physical and chemical properties, but also on the site of initial deposition. The presence of a nonparticulate irritant or the coexistence of a diseased state in the lungs may alter the efficiency of clearance mechanisms, and thus prolong or decrease the residence time of particles in a given area of the respiratory tract. Kotin and Falk (1968) emphasized the possible importance of this interaction in the pathogenesis of lung cancer.

The overall effectiveness of clearance mechanisms in the lung is well illustrated by the finding that the actual amount of mineral dust found in the lungs of miners or city dwellers at autopsy is only a minor fraction of the total amount of dust that must have been deposited in their lungs during their lives. Gross (1964) estimated that the overall removal of insoluble inert particles from the lung is 99% efficient. The retention of 1% accounts for the grey or black discoloration of the adult lung seen at autopsy (Rivers et al. 1960).

3.6.2 CLEARANCE MODEL

The ICRP Task Group on Lung Dynamics (ICRP 1966) considered the respiratory clearance of particles, as well as their deposition, and the model they developed provides a convenient starting point for discussion of experimental work on clearance (see Figure 3-4). The use of this model requires a knowledge of the values for two parameters for each of the pathways described, namely (i) the amount of material residing in the compartment which follows a particular exit path (regional fraction); and (ii) the rate at which that fraction of the material is cleared (biological half-time). Clearance mechanisms can be divided broadly into (i) those depending on ciliary action; and (ii) those which operate in the virtually nonciliated pulmonary region.

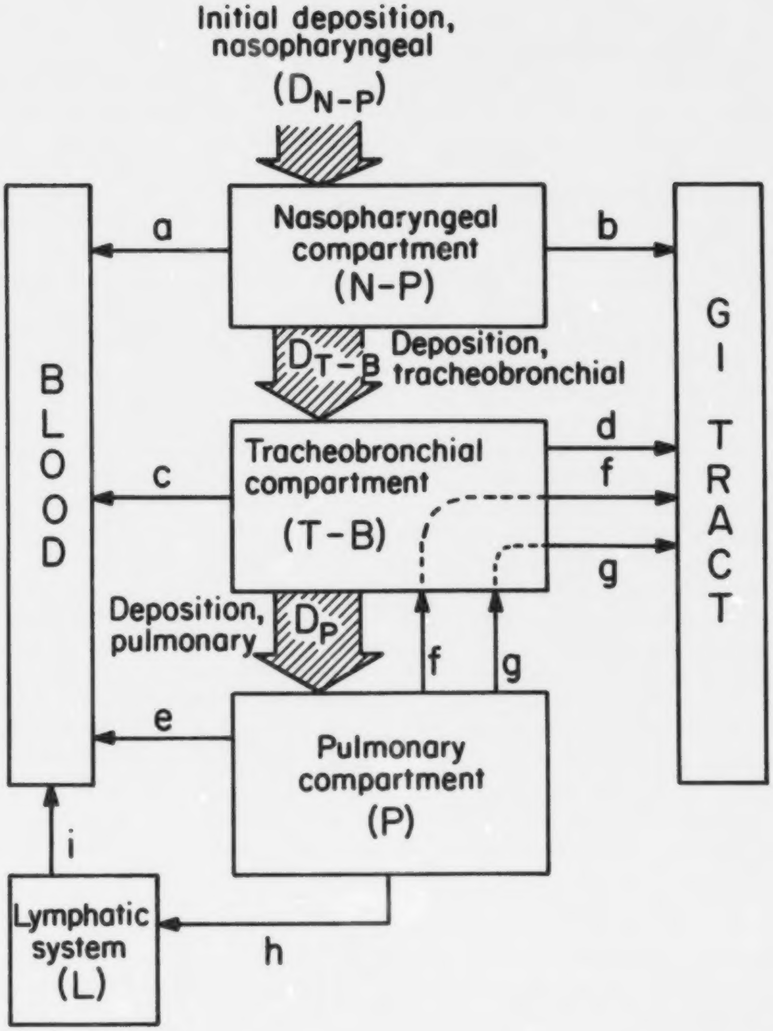
Initial deposition, nasopharyngeal
(D_{N-P})
a
Nasopharyngeal compartment
(N-P)
b
BLOOD
GI TRACT
D_{T-B} Deposition, tracheobronchial
Tracheobronchial compartment
(T-B)
c
d
f
g
Deposition, pulmonary
D_P
f
g
e
Pulmonary compartment
(P)
i
Lymphatic system
(L)
h

Figure 3-4. The ICRP clearance model. Pathways are as follows: (a) material taken up into bloodstream; (b) material rapidly cleared by mucociliary transport; (c) material rapidly absorbed into systemic circulation; (d) material rapidly cleared by mucociliary transport to gastrointestinal tract; (e) translocated or absorbed to bloodstream; (f) rapid clearance phase, presumably by macrophages and mucociliary activity; (g) second slower pulmonary clearance phase dependent on endocytosis and mucociliary transport; (h and i) pathway for clearance by way of lymphatic system.

Following initial deposition in the nasopharyngeal (N-P) compartment (D_{N-P}), material is rapidly taken up into the systemic blood (a), rapidly cleared by mucociliary transport (b), or deposited in the tracheobronchial (T-B) compartment (D_{T-B}). Dust deposited in T-B is rapidly absorbed into the systemic circulation (c), rapidly and quantitatively cleared by mucociliary transport into the gastrointestinal (GI) tract (d), or deposited in the pulmonary (P) compartment (D_P). Some dust is directly translocated from P to the blood (e). The pulmonary compartment exhibits a relatively rapid clearance phase (f) which presumably depends upon recruitable macrophages, which is in turn coupled to the mucociliary transport process. Therefore, the dust cleared by (f) goes to the GI tract via T-B. A second pulmonary clearance process (g) is typically much slower than (f) but still depends upon endocytosis and mucociliary transport, and the cleared dust again goes to the GI tract via T-B. The important distinction is that the clearance is apparently rate limited in the pulmonary region by the nature of the deposited dust. Dust is also slowly removed from the pulmonary compartment (h) via the lymphatic system (L), a process which is qualitatively similar to (g) except that lymph transport replaces mucociliary transport. Finally, dust cleared by the lymphatic system (h) is introduced into the systemic blood by a pathway (i) which obviously depends upon the ability of the cleared material to penetrate the lymph tissue, expecially the lymph nodes. This implies dissolution of the dust particles, partially or completely, but the turnover of lymphocytes may contribute.

3.6.3 CLEARANCE FROM THE NOSE

Once particles have been deposited in the nose they can be removed only by sneezing, blowing the nose, irrigation by nasal discharges stimulated by infections, or using nasal washes. It therefore seems likely that size, shape, site of deposition, and the chemical properties of the particles will determine how long they will be retained, and will influence their ability to produce adverse biological reactions at the site of deposition. Perforation of the nasal septum has been reported in Canadian potash miners (Williams 1974). An increased risk of nasal tumor occurs among certain woodworkers (Acheson _et al_. 1967) and nickel refiners (Doll _et al_. 1977). The residence times for particles deposited in the nose as a result of breathing ambient air are not known. Nevertheless, the long period from the first exposure to wood dust to the detection of a tumor suggests that the residence time of some dusts may be long; repeated exposure may also play an important role.

The fact that resistance across the nose and mouth varies from person to person may account for individual differences in biological response, both in the nose and deeper in the respiratory system. Fry and Black (1973) found that 83% of inhaled particles of diameters 5, 7, and 10 µm were deposited in portions of the nasal areas that were cleared with biological half-times of more than 12 h. Studies with nose-only inhalation in large experimental animals indicated retention times in the nasal turbinates or head of the order of weeks in some cases (Stuart 1966; Newton and Latren 1971). For specific occupational groups in which excess of nasal tumors has been demonstrated, it would be useful to know in greater detail the period of retention of particles in the nasal passages.

3.6.4 CLEARANCE FROM THE TRACHEOBRONCHIAL COMPARTMENT

A sheet of mucus, also called the "mucous blanket" or "mucous lining", covers the surface of the tracheobronchial compartment. This sheet has been recently shown to be discontinuous and formed of particles of mucus 4-10 μm in diameter in the small airways. These particles of mucus reach 70-100 μm in diameter, and are termed flakes in the larger bronchi (Van As 1977). The mucus is kept in a continual upward movement by ciliary activity of the columnar epithelial lining, which extends down as far as the terminal bronchioles.

The frequency of the ciliary beat has been found to be 1,300 min^{-1} in rats (Dalham 1961), while the overlying mucous fluid moved at an average rate of 13.5 mm.min^{-1} in the excised trachea. Rates of mucous fluid movement of 18 mm.min^{-1} in intact animals have been reported by Antweiller (1958). These transport rates seemed to be unaffected by size, mass, or shape of the particles studied, which included soot, coal dust, lycopodium spores, cork dust, aluminum powder, glass, and lead spheres. The only exception was glass spheres, which appeared to be sufficiently smooth to allow the mucus to flow over them rather than to transport them (U.S. Department of Health, Education and Welfare 1969). Gore and Patrick (1978) demonstrated that the mean mass of radiolabelled particles (mass median aerodynamic diameters between 2.4 and 2.8 μm) was cleared more slowly from the extrapulmonary bronchi and first bifurcation over 0-8 d after inhalation than was the corresponding mean mass on the trachea.

Techniques for measuring mucociliary clearance in man are reviewed by Pavia _et al_. (1980).

3.6.5 CLEARANCE FROM THE ALVEOLAR SURFACE

The fraction of an inhaled aerosol which is retained in the respiratory system and the depth to which it penetrates before deposition are related to aerodynamic diameter and shape of particles. With nearly symmetrical particles, such as silica, few particles with diameters larger than 5 μm penetrate to the alveoli.

Particles deposited on the alveolar surface may be removed by any or all of the mechanisms given in the clearance model (see Figure 3-4). They may also become sequestered by a tissue reaction within the lung (e.g. pneumoconiosis), or become bound to protein material in the lungs. Of the several clearance mechanisms, the most rapid is that involving recruitable macrophages (phagocytic cells contained in the alveolar surface epithelium). Phagocytosis may also serve to render the particles incapable of injuring or irritating the alveolar surface epithelium, and may to some extent prevent the penetration of the particles into the interstitium of the lung.

To be an effective alveolar scavenger, the macrophage should be capable of rapid proliferation in response to an unusually heavy load of inhaled particles. Brain (1971) has shown that the total output of free alveolar macrophages is very finely tuned to the effective load of particles that reaches the air sacs. The macrophage output is affected by the particle size, the total load, and the chemical composition of the particle. In his experiments, Brain examined the influence of particle size on the number of free cells found in the lung washings after intratracheal injections of suspensions of coal dust particles with diameters less than 0.053 μm and more than 0.25 μm. The number of free cells, more than 80% of which were mononuclear macrophages, was almost double in the animals injected with the smaller particles than in those injected with the larger particles. LaBelle and Brieger (1961) demonstrated that the number of free phagocytes washed out of the lungs was related to the dust load, and that the amount of dust eliminated from the lungs during the early postexposure period was proportional to the number of free phagocytic cells present. As with most adaptive responses, this clearance mechanism can become saturated. At this point, particles may be observed in the cytoplasm of the type I epithelial cells of the alveolus and later in the interstitial tissue. This may explain why, under conditions of heavy and continuous exposure (e.g. in a coal mine), the dust is not completely eliminated and accumulates in the interstitium of the lung.

The fibrogenic response in pneumoconiosis is related to total load, particle size, and the physiochemical state of the respired aerosol. The variable reactions obtained with different aerosols may be explained, at least in part, by the initial response or lack of response of the alveolar macrophage to the material it has ingested. Camner et al. (1977) studied lung clearance in rabbits during the first week after inhalation of 4-μm Teflon particles tagged with ^{51}Cr and coated with silver, carbon, or beryllium. They concluded that the mechanical removal of intact particles is independent of their chemical structure, given the size of particles and lung burden in their experiment, since clearance for highly toxic beryllium-coated particles was similar to that for the innocuous silver-coated particles.

Inhalation of a test aerosol of 4-μm Teflon particles tagged with ^{111}In by ten healthy nonsmoking men revealed that retention in the lungs decreased greatly in the first day but remained the same between days 1 and 4 (Camner and Philipson 1978). Camner and Philipson (1978) suggested that mucociliary transport in the tracheobronchial compartment accounts for the initial decrease in retention, and that alveolar deposited particles are cleared so slowly that retention changes are not noticed in the next 3 days.

3.7 INFLUENCE OF PARTICLE SIZE AND SHAPE ON CLEARANCE

In experimental studies of respiratory tract clearance, use has been made of monodisperse aerosols tagged with radioactive substances to permit the subsequent fate of the material to be followed by external counting techniques. Albert et al. (1967) studied the clearance from human lungs of 3- and 5-μm iron oxide particles tagged with ^{51}Cr and ^{198}Au. The rapid phase of clearance was completed within 1 d, and in most cases within 12 h. Camner et al. (1971) showed that differences in clearance rates in the same individual were small for monodisperse particles of fluorinated ethylene propylene (approximately 7 μm in diameter), while rates between different individuals differed appreciably.

Holma (1967) generated a "di-disperse" aerosol of 6- and 3-μm polystyrene particles, tagged respectively with ^{198}Au and ^{46}Sc, and measured the simultaneous clearance of the two sizes of particles in rabbits. The larger particles cleared more rapidly than did the smaller particles. The mean half-life for the initial phase was 0.48 h for the 6-μm particles and 1.07 h for the 3-μm particles. The respective half-lives for the long clearance phase were 69.7 and 210 h, respectively. The results of the analysis showed that the differences in the rate of clearance for the two sizes of particles could be attributed to the fact that a larger quantity of 6-μm particles was deposited in the tracheobronchial part of the respiratory tract.

Camner and Philipson (1971) studied the effect of particle size on the clearance processes in two persons, using particles with actual diameters of 4.9, 6.7, and 7.8 μm and an inhalation rate of 1.2 $L.s^{-1}$. Clearance increased with particle size, even for such a narrow particle size range.

Evans et al. (1973) studied the deposition and clearance of UICC radioactively labelled crocidolite asbestos in rats using brief nose-only exposures. Animals were sacrificed serially following administration of the asbestos. The distribution of fibers within the airways and parenchyma was studied by autoradiographic techniques and the amount of material removed from the lower respiratory tract calculated by integrating the long-term component of fecal excretion. An average of 35% of inhaled asbestos was deposited, especially at bifurcations of smaller bronchioles. Fibers in the lung parenchyma tended to occur at the ends of alveolar ducts and at the entrances to alveolar sacs, although some fibers were found in the alveoli. These fibers were shorter (<10 μm in length) and thinner than those deposited in the bronchioles. After 30 d, about 30% of deposited crocidolite remained within the lungs, the remainder having been excreted in the feces.

Particle size and shape are important in clearance from the alveolar surface, because shape and particle dimension may hinder phagocytosis. Allison (1973) examined the limit to the size of particles that could be ingested by phagocytes, using fractions of chrysotile and crocidolite asbestos containing high and low percentages of short fibers. Independently of asbestos type, short fibers (<5 μm) were rapidly and completely taken up by phagocytosis, whereas long fibers (>20 μm) were never completely taken up. The macrophages were closely attached to, or enveloped the ends of, the long fibers, but part of the asbestos fibers remained outside the cells. With long fibers, two or more cells could be seen attached to a single fiber, sometimes with apparent continuity of cytoplasm, and the presence in the culture of multinucleated cells containing long fibers suggests that the process may lead to cell fusion. Particles of intermediate size (5-20 μm) were sometimes completely ingested.

Timbrell and Skidmore (1971) found that the initial retention curve for spherical glass particles in rat lungs resembled the penetration curve of a horizontal elutriator with a 50% penetration of glass spheres of 2-μm diameter. For fibers, length was a major factor in their retention in the lungs. There was a change of slope in the retention curve at about 20-μm fiber length, which could possibly be explained by a lower efficiency of the clearance mechanisms for longer fibers. Such a lower efficiency might be hypothesized on the basis of Allison's observations with macrophages (Allison 1973). There was no clear difference between the rate of retention of straight and curved fibers and fiber aggregrates in the lungs; the influence of fiber length was so great that the effect of fiber shape and secondary dimensions could not be adequately assessed. This suggests that once fibers, because of narrow diameters, have penetrated into the lung, their removal is then dependent on length.

3.8 OTHER FACTORS AFFECTING CLEARANCE

3.8.1 PARTICULATE LOAD

Inhalation experiments using dogs and cats (LeBouffant 1971) have shown that lung clearance depends on the nature of the aerosol and differs from one species to another. The inhalation of coal dust, even in small quantities, leads to a decrease in alveolar clearance in cats; with heavy doses, the clearance becomes very small and does not recuperate appreciably. Inhalation of quartz particles decreases the clearance temporarily, and a long time after quartz inhalation the alveolar accessibility diminishes because of quartz lesions.

3.8.2 OTHER PARTICLES

Camner et al. (1973) studied tracheobronchial clearance in men using 6-μm Teflon particles tagged with ^{99}Tc. Men inhaled the particles with and without carbon dust. Clearance was found on average to be significantly faster when carbon particles were inhaled with the Teflon, indicating an increase in mucociliary transport.

Amosite and chrysotile asbestos exposures of relatively short duration (1-3 h) and high concentration depressed the alveolar clearance of titanium dioxide particles in rats. The effect was not observed when the concentration of asbestos in air was below about 10 times the threshold limit value (estimated to be 0.1 $mg.m^{-3}$) (Ferin and Leach 1976).

3.8.3 MULTIPLE EXPOSURES

Experiments with multiple inhalations have shown a reduction of clearance, with increased biological half-time, for uranium dioxide (Downs 1967).

Ferin (1971) found a higher value of clearance 8 d after multiple inhalation exposures of SO_2 and NO_x than after a single inhalation. Clearance rates were lower in rats with papain-induced emphysema.

3.8.4 INFLUENCE OF IRRITANT GASES

The effect of irritant gases on clearance of particles is of significance where air pollution involves exposure to more than one agent. Exposure of rats to SO_2 (10 ppm, 10 $h.d^{-1}$) accelerated the slower phase of lung clearance of particles during the first six weeks of exposure, but this effect diminished during the next four weeks. Chronic exposure of rats to SO_2 slowed down or caused complete cessation of the transport of tracheal mucus, but the average beat frequency of cilia was the same as in normal animals; the cessation of clearance was the result of an increase in the thickness of the mucous layer from 5 to 25 μm (Dalham 1961).

3.8.5 SMOKING

Albert _et al_. (1971), studying the influence of smoking on tracheobronchial clearance in donkeys, showed a dose-dependent impairment of clearance after acute exposure. In humans, the effects of cigarette smoking were characterized by a pronounced delay in the onset of clearance, followed by a steady progression towards completion. Similar results were obtained by Sanchis _et al_. (1971), who demonstrated a slower first phase of tracheobronchial clearance in smokers, followed by an accelerated second phase.

Cohen _et al_. (1979) found that one year after inhalation of trace amounts of magnetic dust Fe_2O_3, 50% of the dust remained in the lungs of smokers, whereas nonsmokers retained only 10% after one year. Experiments dealing with mucociliary clearance rates in smokers as compared with nonsmokers are reviewed by Pavia _et al_. (1980).

3.8.6 INFECTIONS

Creasia et al. (1972, 1973) demonstrated the effects of experimental influenza virus infection on pulmonary clearance by using chromic oxide dust tagged with ^{51}Cr. A marked deficiency in pulmonary clearance was noted when $^{51}Cr_2O_3$ was administered simultaneously with, or 1, 3, 5, 9, or 56 weeks after, virus inoculation. The distribution of retained chromium in the lungs of infected animals was found to be dependent on the relationship between time of infection and time of administration of chromium. This relationship suggested that there would be an increased risk from exposure to toxic and radioactive aerosols for persons with respiratory infections. This has wide implications when considering the health effects of community air pollutants, as particle concentrations are often high in winter periods which often coincide with epidemics of influenza or other viral infections.

3.8.7 IMPAIRED RESPIRATORY FUNCTION

Thompson and Pavia (1973, 1974b) and Pavia et al. (1980) observed a faster clearance in subjects with impaired respiratory function; the fastest clearance was noticed in subjects with obstructive lung disease, the restrictive group was intermediary, and the "normal" group was the slowest. However, within each of these groups no differences were found in the rate of clearance between smokers, nonsmokers, and ex-smokers. The mean retention at 6 h for 5-μm particles was 53% in bronchitics compared with 70% in a healthy group. Scintigrams in a subject suffering from asthma indicated faster clearance due to restricted penetration rather than an enhanced rate of removal of secretions.

3.9 TRANSLOCATION OF PARTICLES

A characteristic of inhaled particles which has not been fully explained is their penetration to the parietal pleura of the lung. Taskinen et al. (1973) described a hypothesis for the lymphatic transport of inhaled particles to the parietal pleura. The autopsy of a moulder who had been employed for 41 years in iron foundries showed heavy mixed dust (coal and silica) pneumoconiosis. In the parietal pleura there were black linear streaks following the course of intercostal arteries which were microscopically interpreted as periarterial lymphangitis and fibrosis caused by the dust. A retrograde transport of particles via thoracic and intercostal lymphatics seemed to be the best explanation of their findings (as compared with the transpleural route or the propagation through blood vessels). Such a retrograde flow has been mentioned earlier in connection with silicosis and other pneumoconioses. The mechanism was considered to be the same for the transport of small asbestos particles causing pleural plaques (Meurman 1968).

Nagelschmidt (1965) and Hourihane et al. (1966) also reported observations of material resembling asbestos on the parietal pleura, but could not explain its presence. Selikoff (1965) reported that the localization of pleural calcifications in the anterior mediastinal pleura corresponds to the course of lymphatic vessels. Sebastien et al. (1977), based on their studies of fibers in tissues, claimed that only short fibers migrate via the lymphatic system to the pleural surface. In view of the importance of such findings, more work is needed to supplement these reports.

In experimental studies, Kanazawa et al. (1970) injected subcutaneously crocidolite asbestos fibers suspended in physiological saline into one or both flanks of mice. Control mice received an injection of saline only. Most animals were killed at intervals of between 2 and 42 d after injection, but some were left for longer periods up to 623 d. At autopsy, many lymphoid and nonlymphoid structures were removed and examined for the presence of asbestos. Electron microscopy was essential for detecting small fibers and for locating them in specific intracellular structures. Morphological findings indicated that some migration of asbestos fibers from the initial site of injection had occurred. Dissemination was usually along lymphatic pathways, and fibers tended to accumulate in the lymphoid tissues, particularly in the regional axillary lymph nodes; smaller amounts were found in inguinal, mediastinal, and lumbar nodes. The fibers were usually intracellular, lying inside the phagosomes of macrophages, but larger fibers were sometimes encountered lying free. Small numbers of fibers were seen in the spleen as well as in such nonlymphoid organs as the liver, kidneys, and brain, suggesting that some asbestos may enter the bloodstream. There was no evidence of massive or selective spread to subserosal tissues in the thorax or abdomen, although trapping of asbestos fibers was observed in pleural "milky spots" in long-term survivors. A possible role of milky spots in the development of pleural plaques and mesothelioma was suggested. The extent to which increased pressure or disruption of the normal structure of the tissues following injection of relatively large amounts of asbestos influences translocation in such an experiment is not known.

3.10 GASTROINTESTINAL DOSE AS A RESULT OF PARTICLE REMOVAL

The material carried upward by ciliary action is swallowed and thereby enters the gastrointestinal tract. It has been shown (Downs 1967) that uranium dioxide, cleared from the respiratory system to the gastrointestinal tract by ciliary clearance, is responsible for the high urinary levels of uranium seen during the first day after exposure to uranium dioxide dust. The possibility of consequences of exposure to relatively high concentrations of an atmospheric pollutant appearing in organs remote from the lungs must not be overlooked. The increased risk of gastrointestinal cancers in asbestos workers may be related to the high dose of inhaled fibers reaching the GI tract after being removed by ciliary action. The exposures of workers where an excess of these tumors were shown to exist were almost certainly considerably higher than those resulting from even the highest reported concentrations of fibers in drinking water[α] or from levels of fibers in ambient air.

[α] Assuming a 2 fibers mL^{-1} concentration of chrysotile asbestos (current standard) as recorded by phase-contrast microscopy, the total concentration will be of the order of 100 fibers mL^{-1}, as approximately 2% of airborne chrysotile fibers are visible by optical microscopy. If all fibers inhaled by a worker are deposited in the respiratory system, the total dose per day = 100 (fibers mL^{-1}) x 10,000 $mL.min^{-1}$ (air breathed) x 60 ($min.h^{-1}$) x 8 ($h.d^{-1}$) = 480 million fibers d^{-1}. Assuming 50% deposition and 1% long-term retention, 238 million of these fibers could be ingested to the stomach, in addition to any daily intake from fibers in local water. Past concentrations of chrysotile asbestos fibers in the workplace where excesses of GI tract cancer have been detected were many times higher than 2 fibers mL^{-1}.

4.0 TISSUE RESPONSE TO INHALED PARTICLES

This chapter considers the parameters which are of importance in a particle's ability to provoke tissue responses which might result in adverse health effects. It is at this stage that particle composition as well as size and shape become important, and it becomes clear that extrapolations from the behavior of one type of particle to another may not always be possible. It should also be noted that while certain tissue responses might be evoked in cell cultures or in experimental animals, it is not always known whether the same effects occur in man, and if they do, the dose required to produce the biological effect is not always known. While the airborne particles to which the public is exposed include viruses, bacteria, household dusts, and industrial pollutants, our knowledge of the biological response to particles is derived mainly from the study of particles encountered in industry, where the conditions of exposure are quite different from those of the general population.

4.1 NATURE OF TISSUE RESPONSE AND CLASSIFICATION OF INHALED PARTICLES

Insoluble inhaled particles are often classified from the point of view of biologic response into two categories: fibrogenic and nonfibrogenic dusts. Gross (1979) indicated that the division between categories is not clear and that the degree of fibrogenic reaction in the lungs may range from severe with some dusts to slight with other dusts. He therefore proposed a more complete classification (Table 4-1) which is in keeping with the accumulated evidence about the variety of possible reactions evoked by inhaled insoluble respirable dusts.

4.2 NONFIBROGENIC OR "NUISANCE" PARTICLES

Nonfibrogenic particles are defined as those which, when inhaled, evoke a tissue response having the following characteristics: (i) the alveolar architecture remains intact; (ii) the stroma is mainly of reticular character and is minimal in amount; and (iii) the tissue reaction is potentially reversible (Gross 1979).

Nonfibrogenic dusts have also been called "biologically inert" or "nuisance" particles, the latter term being preferred because there is no dust which does not evoke at least a macrophage reaction when inhaled. However, even the term "nuisance" appears inappropriate when applied to a nonfibrogenic dust which, after many years of exposure, is associated with lung function changes not attributable to other factors, or which may be irritating to the upper respiratory tract.

A list of dusts which have not been shown to produce fibrosis or other adverse health effects and which are therefore classified as "nuisance" particles is published annually by the American Conference of

Table 4-1. Proposed biological classification of insoluble respirable dusts or fumes (from Gross 1979).

Insoluble mineral dusts causing pneumoconiosis

Fibrogenic dusts

- Highly fibrogenic (asbestos, silica)
- Moderately fibrogenic (feldspar)
- Slightly fibrogenic (fuller's earth)

Nonfibrogenic dusts

- Nuisance dust (soot, barium sulfate)
- Transitory upper respiratory irritant (fibrous glass)
- Chronic bronchitis producer (soft-coal mine dust)

Insoluble mineral dusts not causing pneumoconiosis

- Fibrogenic dusts (beryllium)
- Edema producing (cadmium oxide fume)
- Fever producing (zinc oxide fume)

Insoluble organic dusts

- Producing airway obstruction (byssinosis - cotton, hemp, or jute dust)
- Producing hypersensitivity pneumonitis (dust from vegetation contaminated with thermophilic fungi or other organisms)
- Producing asthma (wood dust)

Insoluble carcinogenic dusts

- Affecting humans (asbestos, radioactive dusts)
- Affecting animals only (beryllium)

Governmental Industrial Hygienists (ACGIH). This list incorporates a permissible industrial level of exposure for a 8-h period of 10 $mg.m^{-3}$ or 30 mppcf[a] of total dust (ACGIH 1981). The ACGIH list for 1981 included the nuisance particles listed in Table 4-2. Even with inert dusts, gross exposures may overload the particle removal mechanisms, and the above list is regularly revised as additional information on materials becomes available.

4.3 FIBROGENIC PARTICLES

At the present time, there is no universally accepted definition of pneumoconioses, diseases which can result from exposure to fibrogenic dusts. The ILO (International Labour Office) 1950 definition considered pneumoconiosis to be a diagnosable disease of the lungs produced by the inhalation of dust, the term "dust" being understood to refer to particulate matter in the solid phase but excluding living organisms (ILO 1976). However, this definition ignored the presence of dust in the lungs when it caused no roentgenographic changes or discernible clinical disturbance (Gross 1979).

The definition proposed at the Spindletop International Conference on coal workers' pneumoconiosis in 1969 and subsequently adopted by the International Labour Office (ILO 1976) specified that "pneumoconiosis is the accumulation of dust in the lung and the tissue reaction to its presence".

More recently, the Task Force on Occupational Respiratory Disease set up by the Canadian Thoracic Society and the Health Standards Directorate, Health and Welfare Canada, retained the more complete definition of pneumoconiosis as "an accumulation of inorganic dust in the lungs, with or without non-neoplastic tissue reactions to its presence" (Health and Welfare Canada 1979). This definition permits a distinction to be made from some kinds of insoluble dusts, organic as well as inorganic, which may cause disease without forming pulmonary dust accumulations that can be demonstrated microscopically. These diseases, which cannot be termed pneumoconioses, include hypersensitivity, pneumonitides, asthma and other immunological disturbances, pulmonary edema, fever, chronic bronchitis, and disturbances of lung function without recognized morphologic alterations (Gross 1979).

Industrial exposure to certain dusts at elevated concentrations are well recognized as giving rise to lung diseases classified as pneumoconioses. Among these are silica and asbestos, and data are available which show that particle size and shape are important in the tissue reactions leading to the health effects of these minerals.

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[a] Million particles per cubic foot.

Table 4-2. ACGIH list for 1981 of nuisance particles (from ACGIH 1981).

Aluminum oxide (Al_2O_3)
Calcium carbonate
Calcium silicate
Cellulose (paper fiber)
Portland cement
Emery
Glycerin mist
Graphite (synthetic)
Gypsum
Vegetable oil mists (except castor, cashew nut, or similar irritant oils)
Kaolin
Limestone
Magnesite
Marble
Mineral wool fiber
Pentaerythritol
Plaster of Paris
Silicon
Silicon carbide
Starch
Sucrose
Tin oxide
Titanium dioxide
Zinc oxide dust
Zinc stearate

4.3.1 REGULARLY SHAPED PARTICLES: SILICA

There are many forms of free silica which appear to carry different risks of silicosis for workers exposed to them, increasing from the truly amorphous form to the high pressure and temperature varieties. The occurrence and natural history of the disease have been reviewed by Ziskind _et al_. (1976) and are not reproduced here. Occurrence of silicosis in Canadian mines has also been reviewed recently by Gibbs and Pintus (1978).

4.3.1.1 Effects of Silica Particles on Macrophages

Once deposited in the lung, the first likely sites of damage by inhaled particles are the macrophages which attempt to remove them (see Chapter 3).

The phagocytosis of silica particles by alveolar macrophages leads to the death of these cells. The particles released after the cell's death are taken up by the other macrophages which are, in turn, killed. In this way, the death of macrophages continues and stimulates collagen synthesis by fibroblasts in the neighborhood. An analysis of the pathogenesis must therefore proceed in two stages: first by determining how silica particles kill macrophages, and second by determining how this effect is related to fibrogenesis.

Marks (1957) showed that the cytotoxic effects of silica can be conveniently reproduced in cultures of peritoneal and alveolar macrophages. It has been established that the relative toxicity of different forms of silica and of different dusts on cell cultures agrees well with the pathogenicity and fibrogenic effects of the dusts _in vivo_ (Marks and Nagelschmidt 1959; Vigliani _et al_. 1961; Heppleston and Styles 1967). This is of prime importance, as most advances in understanding the mechanisms of particle-cell interactions in recent years have resulted from studies on cell cultures.

The "solubility" theory of King _et al_. (1953a) suggested that silicic acid liberated into the tissues from silica particles brought about deposition of collagen, but later observations did not support this interpretation (King 1967). Curran and Roswell (1958) showed that silica particles implanted into peritoneum in diffusion chambers did not induce any fibrogenic reaction, although silicic acid was liberated from the chambers. Vigliani and Pernis (1963) formulated an autoimmune theory of silicosis, but several workers were unable to obtain experimental evidence in support of the hypothesis (Voisin _et al_. 1964).

Allison _et al_. (1963) showed that particles of silica, diamond, and other materials used in experiments on cultures of macrophages were rapidly included in the phagosomes and surrounded by single membranes. Lysosomes became attached to the phagosomes and discharged their enzymes into the phagosomes. At this point, there was no difference between the action of toxic and nontoxic particles. However, after 18 h of incubation, clear differences were apparent. The nontoxic particles and associated enzymes were still enclosed in secondary lysosomes, whereas many of the toxic particles and associated lysosomal enzymes had escaped into the cytoplasm. The macrophages that had ingested nontoxic particles were fully extended and moved about freely, whereas many of those exposed to toxic particles were rounded and immobile. Thus, it was evident that silica particles, unlike nontoxic particles, could react with the lysosomal membranes and make them permeable. Histochemical studies showing the release of peroxidase taken up into the lysosomes of macrophages after treatment with silica have been published by Nadler and Goldfischer (1970). These authors found that several lysosomal enzymes were released into the medium after exposure of macrophages to silica; this was not seen in control cells incubated with nontoxic dusts or with silica coated with a protective material, poly-2-vinyl-pyridine-N-oxide (PVPNO). The release of lysosomal enzymes preceded the release of the cytoplasmic enzyme lactic dehydrogenase and appeared to precede rather than follow cell death.

Stober and Breiger (1968) focused their interest on a stereochemical hypothesis, emphasizing the silanol groups on the surface of silica particles. The formation of hydrogen bonds between silica particles and active groups of the phagosomal membranes has been suggested as the mechanism for rupturing the phagosome.

Based upon the findings that crystalline silica stimulated the production of hydroxyproline in cultured fibroblasts, Heppleston and Styles (1967) suggested that the dying macrophage releases a factor which stimulates the production of collagen. This hypothesis has been challenged by Harington _et al_. (1973) who were unable to duplicate Heppleston's results. The discrepant results have been attributed by Nourse _et al_. (1975) to differences in the culture systems.

Silica particles can interact with a variety of biological membrane systems, including erythrocytes. In view of this, experiments have been conducted to determine if particles of silica could kill outer cellular membranes. Relatively large amounts of free crystalline silica added to macrophages in a saline medium lacking protein resulted in the rapid killing of cells by cell membrane lysis. However, if silica was added to cells in a medium containing serum protein or bronchial washings, this type of surface interaction did not occur. The silica particles were coated with serum protein when taken up into lysosomes, and only when this coating was digested did the underlying silica surface become exposed to interact with the lysosomal membrane (Allison 1971). Most forms of silicic acid in solution were less damaging than crystalline silica particles, which suggests that the rigid structure or surface properties of quartz and other crystalline silica minerals may be important in damaging the cells; the formation of multiple bonds distorts the membrane structure and leads to the breakdown of the membrane.

The reactivity of silica particles has been attributed to the presence of numerous rigid dihydroxyl groups of silicic acid on their surfaces which can act as hydrogen donors in hydrogen bonding interactions with membrane constituents, especially phosphate ester groups (Allison 1973). This is supported by the fact that certain hydrogen donor compounds protect against experimental silicosis (Schlipköter 1970). Harley and Margolis (1961) found that larger colloidal particles of silica were more hemolytic than smaller particles; 3-μm particles were particularly nonhemolytic and seemed able to protect against subsequent exposure to larger particles. This has been interpreted as meaning that small particles which attach to the cell membrane lack sufficient surface area to rupture the membrane.

A further hypothesis involves the tetrahedral structure of silica. Support for this lies in the fact that stichovite, a rare form of SiO_2 which is octahedral in structure, is not cytotoxic or fibrogenic (Brieger and Gross 1967). However, silica does not need to be in a crystalline form to be cytotoxic (King et al. 1953a; Swensson 1967). A shape hypothesis does not stand up to Luhr's (1958) findings that carborundum and diamond dust fail to show macrophage activity even though the particles are angular and sharp. Quartz is more soluble than another form, coesite, but is equally fibrogenic (Brieger and Gross 1966).

4.3.1.2 Mechanisms Involved in Pulmonary Fibrosis Produced by Silica

As mentioned in the preceding section, certain forms of free silica are extremely cytotoxic to the macrophage, and it seems likely that this macrophagic reaction is an initial step in the sequential development of silicotic fibrosis of the lung (Heppleston 1975, 1977). When inert particles or bacteria are phagocytosed, the lysosomal enzymes are discharged into the phagosomes and remain isolated from the cytoplasm. When silica is ingested, lysosomes rupture and enzymes are released into the cytoplasm. With the death of the macrophage, the silica particles are released from the cell. The toxicity of these particles appears to be completely unaltered, and probably accounts for the repeated cycles of phagocytosis, macrophage killing, and release of free silica that result in industrial silicosis (Heppleston 1975).

In a series of experimental studies, Heppleston (1975, 1977) showed that the supernatant of disrupted macrophages cultured in the presence of quartz particles contained an active factor (or factors) which stimulated the production of hydroxyproline by cultured fibroblasts. The active factor(s) appeared to be nonliquid in nature. On the other hand, inhalation of quartz particles by SPF rats led to massive accumulation of liquid in their lungs and, instead of enhancing pulmonary fibrosis, inhibited the formation of mature silicotic nodules (Heppleston 1975). In the natural state, silica released by dying macrophages is reingested by living ones; therefore, to maintain the fibrotic response, a continued supply of macrophages is required, generally in excess of the normal alveolar content.

4.3.1.3 Influence of Particle Size

An understanding of the role of particle size in the genesis of silicosis is important both theoretically and practically, since size affects the access of dust to the lungs, its subsequent clearance, and perhaps the specific toxicity of the retained material (see Chapter 3). Different industrial processes may produce different size distributions of silica dust, and with changing technology it is likely that dusts will become finer. There is extensive experimental evidence which indicates that the inherent tissue-damaging capacity of free crystalline silica increases as particle size decreases. According to the Committee on Occupational Diseases of the Chest (American College of Chest Physicians 1962), quartz particles larger than 10 µm are virtually harmless because they do not penetrate to the alveoli; particles of 1-3 µm produce a typical silicosis, and particles less than 1 µm may give rise to a dangerous atypical silicosis. Since 1962, several researchers (Brieger 1963; King _et al_. 1963; Goldstein and Webster 1966) have reinvestigated the problem. Klosterkoetter (1967) concluded that the particle size range responsible for the fibrogenic effect of quartz dust is between 0.5 and 5.0 µm.

More recently, Kysela _et al_. (1973) demonstrated the effect of particle size using nine different size ranges of particles (from 0.7 to 35.0 µm in diameter). They injected the particles intratracheally into mice (50 mg quartz dust in 1 mL saline solution), and the animals were sacrificed after three months. The wet weight of the lungs increased as the particle size decreased for particle sizes 7-10 µm or smaller. In order to ascertain the relationships between the size of particles and changes in hydroxyproline, total lipids, and phospholipids, quadratic regression curves were determined, expressing the results of the biological tests as percentages of the results in control animals (taken as 100) (Figure 4-1).

In the above experiment, the same mass of dust, independent of the particle size of the dust, was used in each group of rats. This was based on the results of previous reports indicating the importance of the relationship between the mass of quartz dust and particle surface area (Brieger 1963; King _et al_. 1963; Goldstein and Webster 1966). Because all current theories of the toxic action of silica envision that the effect takes place at the surface of the particle, fibrogenicity should vary inversely with increasing particle diameter for equal quantities of dust by mass. On the other hand, for equal numbers of particles, the decrease in fibrogenicity will, according to this view, vary directly with particle size. However, regardless of particle size, the magnitude of damage should be directly proportional to the total surface area of the dust deposit.

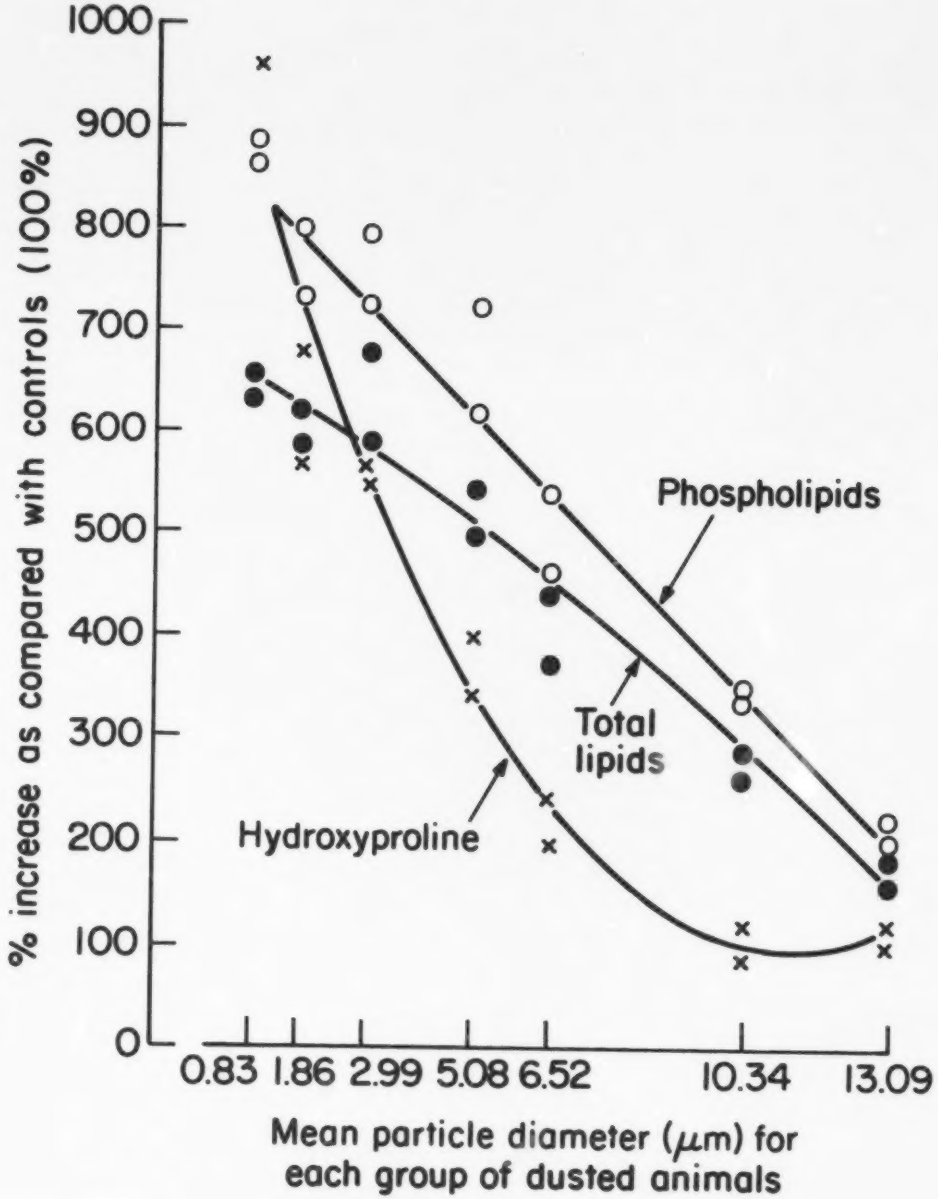

Figure 4-1. Particle size of silica and tissue response (from Kysela _et al_. 1973).

This hypothesis was examined by King et al. (1953b), among others. Graded fractions of flint dust, differing in average size from 8 µm down to 0.05 µm, were injected intratracheally into the lungs of rats in mass quantities adjusted to give equal surface areas in each case. The resulting tissue damage was assessed in terms of histological grading, enlargement of lymph nodes, and amount of collagen formed. Considering the wide range in magnitude of dose by mass (and number), the results gave strong support to this hypothesis. There appears to be an upper limit of biologically significant size. In the submicrometre region, very small particles may be inherently less fibrogenic because they go too rapidly into solution. Particle size, therefore, appears to play a major role in the tissue damage to be expected from silica dusts. Unfortunately, as the qualitative and quantitative assessment of the exposure of workers is difficult, there are no reliable reports of population studies to demonstrate whether the differences in particle size distribution of quartz for the same mass dose produce different effects.

4.3.2 PLATY PARTICLES (MICA AND TALC)

4.3.2.1 Mica

A well-known group of minerals having platy structure are the micas. According to Hamilton and Hardy (1974), there have been reports of pneumoconiosis due to heavy exposure to mica over a period of 5 years or more with cough, dyspnea, and x-ray changes of the lungs. Although mica has been reported to produce pulmonary disease (Heimann et al. 1953; Gupta 1956; Vorwald 1960), the role of potential contaminants (which can include silica) has not been adequately taken into account. A more recent opinion is that sericite mica, as used in industry, does not cause disease (Zaidi 1969).

Experimental studies in rats in which muscovite mica with particle diameter less than 5 µm was used resulted in lesions which consisted of destruction of alveolar architecture and formation of collagen fibers (Kaw and Zaidi 1973). Hemosiderosis was present, and the hemosiderin taken up by phagocytes was considered possibly secondary to the hemolytic action of mica dust on erythrocytes, an effect demonstrated in vitro with free silica and asbestos (Stalder and Stober 1965; MacNab and Harington 1967).

Experimental studies of muscovites and vermiculite showed no long-term effects in animals, but there was an initial slight pathological action with vermiculite which disappeared after several months (Shanker et al. 1975; Swensson 1975).

Intratracheal inoculation of mice with suspensions of mica dusts with particle size below 5 µm was followed by acute inflammatory reaction at early periods, with discrete areas of dust aggregations composed of dust-laden mononuclear cells and formation of fibrils of reticulin (Sahu et al. 1978). Lung tissue was examined for the following 210 d. The histological findings are reported in Table 4-3. It was also found that the transport of mica dust from lungs to lymph nodes occurred earlier than with kaolin or talc.

The small amount of information on mica does not permit any conclusions as to the effect of large platy minerals on tissue, but does suggest that mineralogy and chemistry are likely to be important in consideration of fibrogenicity.

4.3.2.2 Talc

Talc is a hydrated magnesium silicate which in pure form is mainly platy in appearance, and which finds widespread use industrially and domestically. The grades of talc to which the general population is likely to be exposed are somewhat different from those used industrially, in that industrial talcs may or may not be pure talc mineral. The difficulty in determining the true biological effect of platy talc is the possible existence of talc fibers and the common contamination of talc deposits by other minerals, some of which may be fibrous (e.g. anthophyllite, tremolite, and, in some cases, chrysotile) (Rohl and Langer 1974).

In reviewing the evidence concerning the effects of talc on health, Spiegel (1974) concluded that it was well established that some industrial talc exposures could give rise to an interstitial fibrosis, known as talcosis, which is very similar to asbestosis. However, contaminants might be responsible for these effects. Several studies have pointed to asbestos fibers as the pathogenic agent (Rohl and Langer 1974). In addition, free silica may contaminate talc in fairly high concentrations, in which case silicotic lesions could develop. Schepers (1974) in fact concluded that pure talc was biologically inert.

Schritzer and Pundsack (1970), using a red cell hemolysis test, reported that minerals described as "nonasbestiform" fibrous materials, including fibrous talc, produced hemolysis, but other materials studied, including platy talc, were found to be inactive.

Hildick-Smith (1976) reported receiving a personal communication to the effect that commercially available cosmetic grade talc dust did not alter the viability of pulmonary macrophages in rats or interfere with their uptake of colloid particles. This author also reported that there was no difference in incidence or nature of pathological lesions between the control and treatment groups in a study in which hamsters were exposed to 8 $mg.m^{-3}$ respirable cosmetic grade talc for up to 150 $min.d^{-1}$ for 300 consecutive days.

Sahu et al. (1978) inoculated mice intratracheally with talc particles below 5 μm in size. The observed effects on lung tissue are reported in Table 4-4. The data suggest that platy talc itself produces

Table 4-3. Changes in mouse lung tissue following intratracheal inoculation of mica dust (from Sahu *et al*. 1978).

Time after inoculation (d)	Observed effects
15	Many dust-laden macrophage foci together with perivascular and peribronchiolar lymphoid hyperplasia
30	Macrophages showed necrosis and proliferation of fibroblasts
60	Grade I fibrosis developed
90	Increased fibroblastic reaction was seen at the periphery of dust areas and birefringent particles in the corticomedullary zone and medulla
150	Shrinkage of pulmonary lesions and many cholesteral cleftlike structures were observed
	Increased fibroblastic activity
	Infiltration of lymphocytes and slight emphysema
210	Focal areas revealed grade II fibrosis

Table 4-4. Changes in mouse lung tissue following intratracheal inoculation with talc particles less than 5 μm in size (from Sahu *et al*. 1978).

Time after inoculation (d)	Observed effects
15	Large foci of dust deposited in lung parenchyma composed mainly of macrophages and fibroblasts
30	Dust lesions confined to perivascular and peribronchial regions
60	Grade I fibrosis of the interalveolar septum
90	Further fibroblastic proliferation, with many reticular fibers forming a network which penetrated the dust mass
> 90	Fibrotic areas showed further thickening of the interalveolar septa, but did not progress further

minimal cell toxicity, but when the talc is contaminated with significant amounts of either silica or other cytotoxic materials, the tissue response is related to the cytotoxic minerals rather than to the particles of talc.

Epidemiological evidence also suggests that modern mining of cosmetic talc does not appear to be hazardous to health. A retrospective study of the causes of death of 227 talc millers exposed to cosmetic grade talc at the threshold limit value for talc of 20 mppcf for an average of 15.8 years showed that the causes of death were not different from those in a control group of agricultural workers not exposed to talc dust (Rubino et al. 1976).

4.3.3 FIBROUS PARTICLES (ASBESTOS AND FIBROUS GLASS)

4.3.3.1 Asbestos

Six varieties of asbestos are recognized, of which four (amosite, crocidolite, chrysotile, and anthophyllite) are of commercial importance (Hodgson 1965). Tremolite can be a contaminant of certain ore deposits. Because these minerals vary in chemistry, mineralogy, and physical characteristics, it is important to recognize them as separate mineral species; there has been a major failing to do so in the literature. The tissue response to asbestos fibers has been summarized many times in the proceedings of several international symposiums and special review articles (Wright 1969; Allison 1973; Becklake 1976; Miller 1978; Shugar 1979).

The consequences of asbestos fiber inhalation and retention in the human lungs can be fibrosis, bronchogenic carcinoma, mesothelioma of the pleura or peritoneum, or carcinoma at other sites such as the larynx and gastrointestinal tract. This section will deal only with fibrosis.

Asbestosis as an occupational disease was first noted by Auribault (1906) in France, and by Murray (1907) in England. However, its importance was recognized only in 1930 by Merewether and Price (1930). Asbestosis is a chronic progressive disease of insidious onset in which there is diffuse fibrosis of the lung and frequently of the pleural membranes. The disease runs a long course and may lead to death from cardiorespiratory failure. The patients usually exhibit dry cough and breathlessness, depressed vital capacity, and characteristic changes in the chest radiograph. Asbestosis has been shown to occur in persons exposed to all varieties of commercially exploited asbestos.

4.3.3.1.1 Mechanisms Involved in Pulmonary Fibrosis Produced by Asbestos

It is generally accepted that the initial event after inhalation of asbestos, as after inhalation of other particles and fibers, is its attachment to and phagocytosis by macrophages, which play a fundamental role in the pathogenesis of dust disease (Miller 1978). The composition and physical state of the asbestos dust, as well as the dust concentrations in industrial air, may influence the degree of fibrosis as it does the carcinogenic potential (Kleinfeld 1973; Wagner et al. 1974; Davis et al. 1978). Another possibility is that the degree of biological activity relates to the degree of penetration and deposition in the lung, that is, to fiber size and other aerodynamic properties (Miller 1978). Fibers of small diameter can penetrate the lower respiratory tract to different degrees and reach the alveolar spaces where the free-lying pulmonary alveolar macrophages play a key role in the clearance mechanism. By virtue of its phagocytic activity, the macrophage constitutes an essential line of defence against inhaled particles, and the extent to which this defence is breached may determine the appearance of respiratory disease. It is therefore important to study the effects of asbestos particles on the functional integrity of the macrophage, and to see what relevance these effects have on the pathogenesis of dust disease (Miller 1978).

4.3.3.1.2 The Effects of Asbestos Fibers on Macrophages

Most studies of the effects of asbestos on macrophages have made use of peritoneal macrophages which can be maintained *in vitro* under a wide range of conditions, are easily cultured, and are readily obtainable in sufficient quantities for detailed biochemical investigations (Miller 1978). Despite the morphological and biochemical differences between the peritoneal and the alveolar macrophages, their phagocytic and postphagocytic behaviors have been considered sufficiently similar for peritoneal cells to have been used as models for the study of macrophage reactions to exposure to mineral dusts (Leibovich and Ross 1975).

Although the published results on the effects of asbestos on cell cultures are, at times, conflicting (Davis et al. 1978), three general types of effects have been described: acute cytotoxicity, hemolysis, and delayed cytotoxicity (Allison 1973).

In one of the first studies, Pernis et al. (1966) found that neither chrysotile nor crocidolite had any cytotoxic effect on macrophages incubated without serum present in the culture media, whereas the macrophages were fully susceptible to the cytotoxic effect of tridymite (a form of crystalline silica). They suggested that after ingestion of asbestos fibers, and even in the absence of visible cellular damage, the macrophages might release a factor or factors into the surrounding tissue capable of stimulating the proliferation of fibroblasts. This latter fact was obscured by other reports from the same laboratory (Parazzi et al. 1968) showing that both these asbestos types had a marked cytotoxic action on macrophage cultures. However, in this latter study, the crocidolite fibers used were 20-60 μm in length and 3-5 μm in diameter, and the chrysotile fibers were 100 μm in length and 3 μm in diameter; fibers of such length can hardly be incorporated into a macrophage.

In general, different researchers have found crocidolite and amosite to be biologically inactive in most in vitro systems, whereas chrysotile has been found to have a cytotoxic effect on macrophages (Allison 1973; Miller 1978). Some types of asbestos are also hemolytic (Hamilton and Hardy 1974).

Precise comparison of the effects of the different types of asbestos is not possible because size, shape, and surface area cannot be matched. However, a correlation has been made between hemolytic potency, macrophage cytolytic potency, and concentration of magnesium for the various fibers (Allison 1973). The results of studies by MacNab and Harington (1967) suggest that magnesium hydroxide groups known to exist on the surface of the asbestos particles are mainly responsible for their interaction with the cell or plasma membranes (Allison 1973; Miller 1978).

When asbestos particles are added to cultures of macrophages in medium containing serum, they become attached to the plasma membranes of the cells, and fibers of reasonable size are rapidly ingested. Lysosomal hydrolases are then discharged into the vacuoles containing the particles, so forming secondary lysosomes. The subsequent fate of the cells differs according to the culture conditions and type of asbestos, chrysotile being more toxic than amosite or crocidolite at equivalent concentrations (Allison 1971; Bey and Harington 1971; Harington 1976).

Parazzi et al. (1968) concluded from their studies that the physical and mechanical characteristics of asbestos fibers were more responsible than their chemical characteristics for their cytotoxicity. Klosterkoetter and Robock (1975), using the five UICC reference asbestos samples, found that long fibers were more damaging than short ones, probably because of incomplete incorporation of long fibers by macrophages. They concluded that both cytotoxicity and fibrogenicity were probably caused by a mechanical irritation of the asbestos fibers rather than by their chemical composition or molecular structure. As shown by Allison (1973), independent of the asbestos type, short fibers (<5 μm) were readily and completely taken up by phagocytosis, whereas long fibers (>25 μm) were never completely taken up. Longer particles may be coated by an amorphous protein containing ferritin granules to form ferruginous bodies.

The effect of chrysotile asbestos on lung macrophages maintained in organ cultures was observed by Davis (1967), who used pieces of guinea pig lung maintained in organ culture for 10-14 d and chrysotile fibers of 5-μm diameter or less. Electron microscopic examination of the organ culture proved that the asbestos had been quickly taken up by macrophages. During the process of phagocytosis, the number of lysosomes in the macrophages increased considerably, and chrysotile fibers seemed to remain in the phagolysosomes for long periods, although some were also found free in the cytoplasm. Giant cells were observed within 24 h after injection of chrysotile.

The effect of asbestos on macrophages was studied experimentally by Sethi et al. (1974) using glass coverslips implanted in the peritoneum of rats simultaneously with the application of crocidolite fibers. A uniform layer of mononuclear cells containing a large number of small asbestos particles, arranged mostly perinuclearly and lying free in either the cytoplasm or the phagolysosomes, covered the slips within 24-48 h after exposure. Fusion of mononuclear cells was observed at 4 d after exposure, and within a short time many multinucleated cells appeared. It was suggested that the engulfment of solid insoluble particles as such did not provide the necessary stimulation for the fusion of macrophages into giant cells, but rather the fibrous shape and the size of crocidolite asbestos were the essential factors determining the pathogenesis of asbestos (Miller 1978). In another study by Miller and Kagan (1976), very few multinucleated cells were found in the cell suspensions obtained from rats which had received an intraperitoneal injection of UICC crocidolite 5 d previously, and it was suggested that this was due to the fact that the injected fibers were less than 5 μm in length and thus easily phagocytosed by the peritoneal macrophages (Miller 1978). Chamberlain and Brown (1978) demonstrated that, in experiments on tissue cultures, milled crocidolite was less cytotoxic than the standard UICC crocidolite, despite the fact that an equal mass of the milled sample contains many more particles. This suggests that the fibrous morphology of the dust is an important determinant of its cytotoxicity.

4.3.3.1.3 Fibrogenic Effects of Asbestos Fibers

Under proper conditions, a wide variety of inorganic fibers is capable of stimulating the production of collagen in both man and experimental animals. A number of variables influence the extent to which this fibrosis takes place; however, the dominant feature is the reaction of the lung to inhaled fibers. Vigliani (1968) drew attention to the considerable importance of fiber length and fiber diameter and the contribution made to the pathogenesis by ultramicroscopic fibers. There is general agreement that long fibers (>25 μm) are more fibrogenic than short ones (<5 μm) (Wagner and Berry 1973). The type of fiber is also important, as is site of administration to experimental animals. The most realistic way of exposing animals to fibers is by inhalation, because this most closely parallels the human situation.

Davis (1972) found the following mineral fibers to be fibrogenic when injected in the pleural cavity of mice: chrysotile (short fibers, <1 μm long; long fibers, 1-200 μm long), short synthetic fibers, fibrous brucite, and silica fibers. Other fibrogenic minerals included chlorite, chromite forsterite, magnetite, olivine, pyroxene, serpentine, and talc. All materials produced granulomas in the pleural cavities of mice, although there was great variation in the magnitude of cell responses (Table 4-5). From these results Davis concluded that all the foreign material injected stimulated the production of a certain amount of collagen. Two important findings emerged: (i) long-fiber samples quickly produced large cellular granulomas that were eventually replaced by large amounts of fibrous tissue; and (ii) short-fiber samples or nonfibrous dusts and finely ground dusts stimulated much less reaction. Thus, particle size and shape are important properties determining pathological effect. These studies support the contention that longer fibers are more fibrogenic than shorter ones, essentially because the longer ones are less well phagocytosed and translocated (Hilscher et al. 1970; Beck et al. 1971; Timbrell 1973; Harington et al. 1975). The only report that apparently contradicts this conclusion is that of Holt et al. (1965), who produced extensive fibrosis of the lungs in guinea pigs by using very fine particles of asbestos dust. The size distribution was not well described, and local heating from grinding the asbestos was likely to cause changes in composition.

Transport begins with fibers measuring 20 µm and increases with decreasing fiber length. Also, short fibers are almost always found intracellularly (Timbrell and Skidmore 1968), whereas longer ones are seldom incorporated by cells.

In general, the sites of deposition and clearance from the lung influence the way in which fibers of different lengths exert their biological effects. In experiments where the pleural cavity is used, the fibers are artificially deposited in a confined space; in the lung, long fibers deposited by respiration would be difficult to mobilize, whereas short ones could be phagocytosed by macrophages and carried away (Davis 1972). Short fibers would also penetrate more efficiently to the lower parts of the lung. Davis (1972) pointed out that long fibers could cause considerable irritation during constant respiratory movements, whereas short ones would be aggregated into compact masses and probably relatively easily encapsulated.

Timbrell and Skidmore (1968) exposed rats and guinea pigs to long and short fibers of amosite. Twice as much dust was retained in the lungs after exposure to the short-fiber aerosol than to the long-fiber one, because of deeper penetration of the former. In animals that had died more than a year after exposure, lesions consistent with early asbestosis were seen in the long-fiber group, but no progression had occurred in the short-fiber group.

The experimental evidence regarding fiber length and progressive fibrosis can be summarized as follows: longer fibers are probably more effective than shorter fibers in the production of asbestosis in experimental animals. Fiber diameter has received considerable attention and appears to play an important part in deciding depth of lung penetration (Timbrell and Skidmore 1968; Timbrell 1973). Other theories to explain why some fibers cause fibrosis have attributed

Table 4-5. Cellular response to various minerals and fibers injected into the pleural cavities of mice (from Davis 1972).

Mineral or fiber	Response
Chromite, magnetite	Poorest cellular response
Chlorite, ground glass fiber (both thick and thin), ground silica fiber, ground insulation fiber	Similar lesions; amount of collagen much greater than with chromite and magnetite
Talc, serpentine, pyroxene, olivine, forsterite, finely ground brucite	Similar lesions; cellular response extremely good; size of granulomas and collagen production much greater than with above groups
Long fiber group: glass, silica, long brucite, insulation fibers	Largest granulomas of all; collagen production gradual but continuous
Varieties of chrysotile	
Long fiber	Large cellular granulomas; rapid collagen production
Short fiber	Much smaller granulomas; final collagen content much lower than with long fiber
Synthetic	Even smaller granulomas than with short fiber; very little collagen produced

the response either to mechanical irritation by the fibers or to an immune reaction.

A number of studies suggest that impaired T-lymphocyte function occurs in workers with asbestosis (Kang et al. 1974; Kagan et al. 1977; Haslam et al. 1978). Other studies suggest that a genetic factor associated with the HLA antigen locus may influence the development of asbestosis in asbestos workers (Matej et al. 1977; Wagner and Darke 1979). Immunologic abnormalities in asbestos workers have been reviewed by Lange (1980a, b).

Sebastien et al. (1977) showed that the longest fibers found in lymphatics were about 7 µm, supporting the view that they can only be transported via the agency of mobile phagocytes. However, this observation requires confirmation, as the vast majority of inhaled fibers are short and the observation may or may not represent size selection.

The biological hazards related to short-fibered asbestos dust (i.e. <5 µm in length) have been the subject of much controversy (Gross 1974b). Because fibers of this size have numerical preponderance over longer fibers and tend to remain airborne slightly longer, the chances of their inhalation are increased. The fact that these fibers enter the air spaces with the inspired air and come into contact with alveolar membrane does not mean that they are responsible for the reactions in the lung, because long fibers are also present. Several studies suggest that short fibers are less hazardous from the standpoint of causing fibrosis. Experimental studies carried out by Klosterkoetter (1968) showed that chrysotile and crocidolite fibers, ground to an average length of 5 µm, produced no fibrosis when injected intratracheally or intraabdominally, whereas longer fibers of the same asbestos caused fibrosis in both regions.

Other studies by Timbrell and Skidmore (1968), Webster (1970), Smith et al. (1972), Hilscher et al. (1970), and Wright and Kuschner (1977) showed that short fibers produced only minimal pulmonary response or a macrophage reaction in the lungs when inhaled, and produced no fibrous adhesions when inoculated intraabdominally or intrapleurally. Gross (1974b) concluded from these studies that asbestos fibers of length less than 5 µm have neither fibrogenic nor carcinogenic potential.

The extensive experimental studies carried out by Davis (1972) showed that long fibers produce cellular granulomata which form firm adhesions between lungs, diaphragm, and chest wall. When the same mineral samples were more finely ground and sieved so that no long fibers remained, the resulting granulomata were smaller and did not form adhesions. When granular dusts were used, the chemical composition appeared to be more important than size and shape in determining the tissue response. The conclusions of these studies were that the long fibers are difficult to remove once they have reached the alveoli, whereas short fibers and nonfibrous dusts that can be easily phagocytosed by a single macrophage are cleared more easily.

It should be noted, however, that only a few investigators have described the size characteristics of their asbestos dust samples adequately. The dimensions of fibers include both length and diameter, and different methods of fiber preparation may give rise to similar diameter distributions and similar length distributions but different size distributions of fibers when both dimensions are considered together. The intratracheal injection of fibers or the act of rendering them airborne may alter the size distributions of the originally characterized materials, and the dimensions of fibers in the lungs of the experimental animal may also be different. The dose used varies from experiment to experiment, and investigators have not adequately considered whether the observed tissue responses are related to mass or number of fibers. As fibers of different varieties of asbestos have different "minimum" diameters, the same mass dose may reflect major differences in number of fibers (Davis et al. 1978).

The possibility that mineral fibers stimulate fibroblasts directly was examined by Richards et al. (1971) and Richards and Morris (1973). Cultures of rabbit lung fibroblasts were exposed to Rhodesian chrysotile asbestos, fiber glass, coal, glass, and quartz particles. Asbestos was found to increase significantly the amount of collagen in the cell mat as judged by hydroxyproline in hydrolysates; the concentrations of DNA in control and fiber-exposed cultures were not significantly different.

The synthesis and laying down of collagen in vitro is a complex process which can be affected by many variables, including the composition of the medium, the rate of growth of the cells, the proportion of collagen synthesized that is bound in the cell mat, and the breakdown of collagen. Bates et al. (1972) found that only 25-40% of the total collagen produced by fibroblasts in culture was bound to the cell mat, the remainder being released in a macromolecular form into the cultural medium. The results of Richards et al. (1971) and Richards and Morris (1973) raise the possibility that the in vivo fibrogenic effects of asbestos might be exerted directly on fibroblasts; presumably fibers which are large enough to escape engulfment by macrophages would be better able than shorter fibers to stimulate fibroblasts.

A comparison between the in vitro toxicity of dusts of certain polymers and minerals (asbestos, aragonite, polyurethane, and polyethyleneterephthalate (PEP)) and their fibrogenicity (Conning et al. 1971) showed that there is a direct relationship between cytotoxicity to macrophages in culture and fibrogenicity in the living animal, and that this relationship seems to be independent of particle shape, size, concentration, and phagocytic potential. Among the dusts tested, chrysotile asbestos was the most fibrogenic, whereas aragonite (acicular, 1 μm in diameter, 3.5 μm in length) and PEP (0.4-4 μm in diameter) produced only a transient reaction.

4.3.3.2 Fibrous Glass

As a result of the general phasing out of asbestos in insulation products and the experimental evidence that glass fibers of certain dimensions could be carcinogenic in animals, a renewed interest has been taken in the health effects of substitution products for asbestos, of which fibrous glass is the main one. In a broad sense, the term "fibrous glass" encompasses any fibrous material that exists in a glassy state. In other words, if a material exists as a fiber (i.e. if it has a length-to-diameter ratio greater than 3:1) and the ions of which it is composed do not have a well-ordered, regular structure with respect to each other, then the substance is termed "fibrous glass" regardless of its chemical composition. Fibrous glass therefore includes mineral wool and glass wool (Pundsack 1976). Glass fibers are made either by continuous filament pulling in which the fibers are of relatively uniform diameter, or by fluid attenuation in which the fibers vary in length. Typical dimensions of fibers (diameter) used for various purposes have been summarized by Pundsack (1974) (Table 4-6).

Schepers (1955) described bronchial epithelial hyperplasia and endobronchiolar as well as peribronchiolar lesions in rats exposed to fibrous glass dusts. Schepers and Delahant (1955), however, found that glass fibers were not fibrogenic and that they provoked no microscopically detectable reaction in the lung. The Committee on Environmental Health of the American College of Chest Physicians (1976) concluded that the results of animal work showed glass fibers to be non-fibrogenic.

Botham and Holt (1971, 1973) studied the effects of inhaled fibrous glass on the lungs of guinea pigs killed at monthly intervals over 18 months after exposure to dust-laden atmospheres containing glass fibers that ranged up to 0.5 mm in length with a maximum diameter of 3.0 µm, or to glass powder with a maximum particle diameter of 10 µm. The effects on lung tissue are recorded in Table 4-7.

Glass fiber bodies (analogous to asbestos bodies) were found one month after dust inhalation (Botham 1976). However, there was no association of collagen fibers with fragmented glass bodies, and there was little fibrosis of the lungs as indicated by collagen increase (Botham 1976). Most glass fiber bodies were 30 µm in length.

Gross (1976), in reviewing studies on the health effects of fiberglass dust, concluded that no recognizable anatomical or functional changes were associated with inhalation of fiberglass dust. Furthermore, atelectasis did not occur, in contrast to the effects observed after inhalation of other nonfibrogenic "nuisance" particles (Gross 1974a).

Davis (1976) studied the influence of fiber size on the effects of fibrous glass injection into the pleural and peritoneal cavities of mice and rats. All fiberglass samples produced granulomas

Table 4-6. Types of glass fibers available and their respective diameters (from Pundsack 1974).

Type of fiber	Diameter (μm)
Continuous filament	
Plastic reinforcement	6.5-9.0
Textile fibers	5
β-textile fibers	3
Gas attenuated fibers	
Conventional insulation	4-6
Micro fibers	0.03-3.0

Table 4-7. Effect of inhaled fibrous glass on lungs of guinea pigs after inhalation of dust-laden atmosphere containing glass fibers (from Botham and Holt 1971, 1973; Botham 1976).

Time after inhalation period	Observed effects
< 1 d	Extracellular fibers were found in the bronchioles, most shorter than 20 µm; fibers partly ingested by macrophages were found in alveoli, but no free extracellular fibers were found in alveoli
1-7 d	Macrophages containing fibers were common in alveolar ducts and spaces; giant cells containing fibers, desquamated epithelial cells, and red blood cells were found in bronchiolar debris
1 month	No extracellular fibers were found, and most alveolar macrophages were cleared; glass fiber bodies (analogous to asbestos bodies) were found
18 months	All fibers in free macrophages were coated by Perls-positive material; thickening of the interalveolar septa occurred, but this did not lead to obliteration of the alveolar spaces

within the pleural cavity, but these differed in size and structure. Short-fiber samples (less than 20 μm in length) produced small compact granulomas which did not form adhesions. Long-fiber samples (several hundred micrometres in length) produced large granulomas which often filled a large part of the pleural cavity and formed adhesions between lung, diaphragm, heart, and chest wall.

Similarly, Kuschner and Wright (1976) found long fibers (between 10 and 100 μm in length) to cause peribronchial interstitial fibrosis. Short fibers (less than 10 μm in length) caused no fibrosis of the lungs.

These experiments have shown qualitative similarities in the response to asbestos and glass fibers, supporting the contention that it is the physical characteristics of fibers which determine tissue damage, and that the length of the fiber plays an important role. However, it should be recognized that the method of intratracheal injection is artificial, and that an improved inhalation method is required.

Gross (1976) reported an improved inhalation experiment where the results of intratracheal injections were similar to those in animals which had inhaled dust. However, the number and size of the dust foci in the lungs were smaller in the inhalation experiment series.

Some data exist concerning the effects of glass fiber on workers, but the dimensions of fibers to which workers were exposed are generally not known. In a study of 1389 employees of a fiberglass factory, Wright (1968) found no unusual pattern of densities on their chest radiographs. Utidjian and De Treville (1970), who studied workers at the same plant using spirometry, questionnaires, and x-rays, also concluded that workers with heavy dust exposure were no less healthy than those with minimal dust exposure. Pulmonary diffusion studies showed no measurable effect on the diffusion of gases across the alveolar membrane (De Treville et al. 1970). Other studies have supported the apparent lack of effect of fiberglass exposure (Nasr et al. 1971; Hill 1974).

One finding which has not been explained is the apparent excess of deaths from chronic bronchitis among fiberglass workers. A mortality study of 416 retired employees of a fibrous glass insulation plant showed no cause-specific excess mortality except a possible excess in chronic bronchitis (Enterline and Henderson 1975). Bayliss (1974) and Bayliss et al. (1976) also found an excess of deaths from chronic emphysema, cor pulmonale, and chronic bronchitis. The role of smoking was not considered, and this would be important before drawing final conclusions.

4.4 CARCINOGENICITY OF FIBROUS PARTICLES

Until recently, little attention was paid to the possible importance of particle size or shape in carcinogenicity. Most carcinogens were considered to act by direct chemical action or by interference with enzyme systems and cell metabolism. However, the demonstration of increased risks of lung and other cancers among workers exposed to asbestos and the occurrence of primary malignant mesothelial tumors in the general population (see Chapter 5) stimulated research into the carcinogenicity of fibers in general. One important development has been the demonstration that whereas certain biological effects, such as cytotoxicity, are related to the chemical composition of their surfaces, other biological effects, including fibrogenicity and carcinogenicity, are more closely related to fiber dimensions than to their chemical composition (Wagner and Berry 1973).

The most complete data concerning fiber size and carcinogenicity are derived from studies of the induction of mesothelioma after intrapleural injection or implantation of different types of asbestos and other fibers. Wagner (1962) was the first to report that crocidolite and chrysotile could induce mesothelial tumors in rats after intrapleural inoculation of fibers. Furthermore, for chrysotile and crocidolite, there was a relationship between the dose of fiber inoculated and the number of mesotheliomas induced (Wagner and Berry 1969). Wagner et al. (1973, 1974) studied the frequency of lung tumors and mesothelioma in rats which inhaled different types of asbestos dusts for periods of time ranging from 1 d to 24 months. In the inhalation study, all types of fibers produced asbestosis and fibrosis which progressed after the end of exposure. All samples including anthophyllite produced an excess of lung tumors. Mesotheliomas were found in animals exposed to crocidolite, amosite, Canadian chrysotile, and anthophyllite. The number of animals developing lung tumors after inhalation of various types of asbestos fibers is shown in Table 4-8. The percentage of rats developing mesothelioma after intrapleural inoculation of various materials is given in Table 4-9.

Chemical composition of asbestos fibers appears to be a minor factor in carcinogenicity, which is consistent with the hypothesis that carcinogenicity is related to the ability of fibers to interact with the cell membrane without destroying the cell (Harington 1976). A relationship was found between carcinogenicity and size distribution of fibers. The UICC amphibole samples tested had diameter distributions which, in decreasing order of fineness, were crocidolite, amosite, and anthophyllite. Thus, for a given weight of asbestos inoculated into the pleural cavity, anthophyllite provided fewer fibers than did amosite, which in turn provided fewer fibers than did crocidolite. Of these fibers, only a small proportion of anthophyllite would be below the threshold diameter, whereas the proportion of amosite would be somewhat larger and that of crocidolite still larger. This classification of the amphiboles is in the same order as the efficiency with which they produced mesotheliomas in the experiment. Thus the fibrous nature of the materials used appeared to be a major factor in the production of mesotheliomas: the finer the fiber, the more tumors produced (Harington 1976).

Table 4-8. Number of animals developing tumors after inhalation of various materials (from Wagner 1976).

Dust	No. of animals	Adenocarcinomas	Squamous carcinomas	Mesotheliomas
Amosite	146	5	6	1
Anthophyllite	145	8	8	2
Crocidolite	141	7	9	4
Chrysotile (Canadian)	137	11	6	4
Chrysotile (Rhodesian)	144	19	11	0
Controls	126	0	0	0

Note: Rats were exposed to asbestos samples at concentrations of about 12 mg.m^{-3} of respirable dust for different lengths of time.

Table 4-9. Percentage of rats developing mesothelioma after intrapleural inoculation of various materials (from Wagner 1976).

Material	% of rats with mesotheliomas
SFA chrysotile[α]	66
UICC crocidolite	61
UICC amosite	36
UICC anthophyllite	34
UICC chrysotile (Canadian)	30
UICC chrysotile (Rhodesian)	19
Fine glass fiber (code 100)	12
Ceramic fiber	10
Glass powder	3
Coarse glass fiber (code 110)	0

Note: 20 mg of the various materials were inoculated into the pleural cavities of rats.

[α] This was a very specially prepared chrysotile sample.

Studies by Stanton and Wrench (1972) suggested that fibers about 20-200 μm in length and between 0.5 and 5 μm in diameter are more effective in inducing mesotheliomas than are larger or smaller fibers. They demonstrated that reducing the size of crocidolite fibers by pulverization, a process which increases the number of submicroscopic fibrils of asbestos, reduced the carcinogenicity. These workers concluded that pulverized crocidolite of sizes less than 1.25-3.75 μm could be discounted as far as mesothelioma production was concerned.

Wagner et al. (1973) found fibers less than 0.5 μm in diameter and longer than 5-10 μm likely to be more important in mesothelioma production in rats, while Wagner and Berry (1973) found a sample of Canadian chrysotile with very short fibers to be highly efficient in mesothelioma induction. Timbrell (1973) interpreted this result to support the idea of a threshold length necessary for mesothelioma production, but the interpretation is complicated by possible changes in fiber structure associated with the fine milling and inadequate published data on fiber dimensions. Similar results have been obtained in experimental studies in which fibrous particles other than asbestos have been used. In comparing the results of implanting different glass fiber samples on the pleura, Stanton and Wrench (1972) found that samples which were composed over 90% by weight of fibers less than 2.5 μm in diameter were more carcinogenic, and, as length was reduced, carcinogenicity was also reduced. The importance of structure and shape of particles in determining carcinogenicity became apparent in experiments using fibrous and nonfibrous forms of aluminum oxide (Al_2O_3). The fibrous forms carried the same carcinogenic hazard for the pleura as did asbestos and glass fibers, whereas the nonfibrous material did not yield any mesothelioma. Stanton and Wrench (1972) and Stanton (1973) concluded that the carcinogenicity of asbestos, glass fibers, and aluminum oxide (Al_2O_3) is primarily related to the length and diameter of fibers rather than to physicochemical properties; exceptionally pure, chemically inert fibers composed of asbestos-free material and glass seem to carry the same hazard for the pleura as do asbestos and glass. Thus it appears that carcinogenicity is related to a durable fibrous shape and, possibly, narrow size range (Harington 1976).

Pott et al. (1976) inoculated mice intraperitoneally with different sizes of glass fiber dust and crocidolite fibers. In agreement with the results of Stanton (1973), they concluded that both diameter and length of fibers used were important in determining their carcinogenic effect.

In a series of experiments conducted with the same technique, Stanton et al. (1977) studied the carcinogenicity of fibrous glass by implanting intrapleurally in rats a standard dose of 40 mg test fibers suspended in 1.5 mL of 10% gelatin. Seventeen samples of different diameters and lengths were studied and classified according to the probability of pleural carcinoma developing between 53 and 104 weeks after inoculation. The group of fibers with the highest carcinogenic potential (i.e. 64.4-85.3%) consisted of samples less than or equal to

1.5 μm in diameter and greater than 8 μm in length. The experiment indicated that decreasing diameter and increasing length were related to carcinogenicity.

The question arises whether there are any known properties of cells that allow them to react to the dimensions of solid bodies. Except under special conditions, fibroblasts require the support of a solid substance for growth. Growth in suspension does not occur unless the cells can be attached to solid particles above a critical minimum dimension. This property has been termed "anchorage dependence" (Bischoff and Bryson 1964). Maroudas et al. (1973) found that no growth occurs for fibers of length 20 μm or less, and stimulation increases with fiber lengths up to about 200 μm. The authors postulate that solid foreign bodies induce two basic types of hyperplastic reaction, according to size. The effect of fibers longer than 40 μm depends on anchorage, which predominantly stimulates mesenchyme, whereas particles below 20 μm in length stimulate only mononuclear phagocytes. It seems possible that fiber carcinogenesis is a modified form of solid state carcinogenesis.

An in-depth review of the relationship of asbestos to mesothelioma production has been published by Kannerstein et al. (1978).

4.5 INTERFERENCE BY PARTICLES IN RESPONSE TO THE INHALATION OF GASES, DROPLETS, AND OTHER AIR CONTAMINANTS

Dautrebande (1939) reported that concentrations of mustard gas which were relatively harmless to rats would produce edema when administered in combination with an inert aerosol such as sodium chloride. LaBelle et al. (1955) studied the effect of particulate matter on the survival time of mice exposed to formaldehyde, acrolein, and oxides of nitrogen. They found that gases which were more readily absorbed in the respiratory tract when adsorbed on small particles would tend to be carried into the lung, and hence the toxicity would be increased. However, the fact that ammonia and carbon particles did not produce the same results suggests that the mechanism is more complex (Dalham and Reid 1967). Pattle and Burgess (1957) found that the inhalation of smoke by mice and guinea pigs prior to inhalation of sulfur dioxide reduced the toxicity of sulfur dioxide as measured by the dose required to produce death, whereas the toxicity increased when mixtures of SO_2 and smoke were inhaled. The mechanism for the reduction in toxicity was considered to be possible stimulation of the mucosa by the smoke or possible reduction in the volume breathed following smoke inhalation which would reduce the sulfur dioxide dose.

Furthermore, Salem and Cullumbine (1961) found that kerosene smoke reduced the toxicity of acrolein and acetaldehyde. Wagner et al. (1961) found that the exposure of mice to oil mists protected them against later inhalation of ozone and nitrogen dioxide. When oil and ozone were given together there was an enhancement of toxicity. In a series of experiments, Amdur and Corn (1963) showed that zinc ammonium sulfate could produce an increase in flow resistance in guinea pigs similar to that produced by inhalation of sulfuric acid droplets (Amdur 1958). No airway resistance increase was found with particles of diameter less than 0.5 µm of a wide range of materials, including carbon (8 mg.m^{-3}), activated carbon (8.7 mg.m^{-3}), manganese dioxide (9.7 mg.m^{-3}), open hearth dust (7.0 mg.m^{-3}), iron oxide (21.0 mg.m^{-3}), manganese chloride (1 mg.m^{-3}), ferrous sulfate (1 mg.m^{-3}), and sodium orthovanadate (0.7 mg.m^{-3}) (Amdur and Underhill 1968). In contrast to the above particulates, sulfuric acid droplets have been observed to be active. At mass concentrations between 1.4 and 1.9 mg.m^{-3}, sulfuric acid mists of 0.8 mg.m^{-3} produced a 50% increase in pulmonary flow resistance in guinea pigs as compared with normal values, and zinc ammonium sulfate particles of 0.84-µm diameter produced a 21% increase. When zinc ammonium sulfate of particle size 0.3 µm was used, the corresponding increase in pulmonary flow resistance was 130%. These studies showed that as the particle size decreased over the range from 1.4 to 0.29 µm, the response to an equal mass increased (Amdur and Corn 1963). Studies with m-terphenyl (sizes 0.3-2.0 µm) produced a similar size-dependent response, and showed that a small increase in concentration would produce a greater than linear increase in response (as measured by airway resistance) when the particles were smaller than 1 µm (Amdur and Creasia 1966).

For many years, it has been suggested that polycyclic aromatic hydrocarbons in air pollution might play a role in lung cancer (Schoental 1964). However, there have been two major problems in demonstrating such an association. The first problem is the overwhelming effect of cigarette smoking, and the second is the difficulty in excluding from consideration the other factors in the environment which may influence lung cancer mortality. There is some evidence that polycyclic aromatic hydrocarbons cannot be readily eluted from very small particles; in fact, particles with an average diameter of less than 0.04 µm have been reported to remove polycyclic aromatic compounds from their immediate vicinity by high surface adsorption (Falk et al. 1968). Particles above a 0.04-µm average size release the hydrocarbons in the presence of appropriate solvents, including plasma and cytoplasmic proteins. As particle sizes increase, the release becomes more rapid and greater in extent. While the effect of smoking on lung cancer has been studied extensively, there have been few experimental studies on the pathology of carcinogenesis following exposure to air pollutants where particle size has been critically controlled.

In order to determine the possible carcinogenic and cocarcinogenic effects of talc, Stenback and Rowland (1978) studied the biologic and morphologic alterations caused by repeated intratracheal instillations of talc alone or in combination with benzo(a)pyrene in Syrian golden hamsters. The size distribution of talc particles used was as follows: 93.3% below 25 µm, 54.3% below 10 µm, and 25% below 5 µm. Intratracheal instillations were made repeatedly, once weekly, for

18 weeks, the animals being followed up until their death, which was most commonly due to interstitial fibrosis or neoplastic involvement of the respiratory system. In animals instilled with talc alone, histologic investigations revealed pulmonary congestion and interstitial fibrosis in some instances. No detectable dust deposits, granuloma formation, or mesothelial proliferations were found, and no signs of neoplastic transformation were observed in the respiratory system. The group treated with both talc and benzo(a)pyrene developed fibrosis and inflammation in the lungs; in addition, tumors were found throughout the respiratory tract and mainly in the lungs. Many tumors were squamous epitheliomas, papillomas, or squamous cell carcinomas. It must be noted that the small amounts of polycyclic aromatic hydrocarbons (including benzo(a)pyrene) present in the tar collected from cigarette smoking machines, though weakly active when applied on the mouse skin, failed to induce lung cancer under a variety of experimental conditions (Schoental 1964).

4.6 INHALED PARTICLES CAUSING ACUTE RESPIRATORY REACTIONS

Metal fume fevers are acute responses of short duration which occur when fume is inhaled from a metal heated to a temperature above its melting point. It is now known that a number of metals can produce the syndrome, the most common ones being zinc, copper, and magnesium. Aluminum, antimony, cadmium, iron, manganese, nickel, selenium, silver, and tin may also cause metal fume fevers. The acute reaction is thought to be due to the formation of dry fine particles which possess enhanced surface activity (Hunter 1975). Though the etiological mechanism for the reaction has not received much attention, acute reactions in workers of aluminum smelters are considered to be related to fluoride exposure (Field and Smith 1973).

A form of pneumoconiosis known as Shaver's disease was reported in Canada among men exposed to fumes arising during the process of making corundum (Shaver and Riddell 1947). Fumes were released during the smelting of bauxite and there were 13 deaths from pneumothorax. The particle sizes were 0.05-0.5 µm. There have apparently been no reports of cases since that time.

4.7 SYSTEMIC POISONS AND PARTICLE SIZE

Due to the intimacy of contact between the air and blood in the lungs, the respiratory system provides a more effective entry of toxic substances into the systemic circulation and internal organs of the body than does the gastrointestinal tract. This was demonstrated in the case of lead by Aub et al. (1926) who found that 10-20% of the lead injected as particulate $PbCO_3$ into animal lungs was transferred into the blood within a few hours, whereas only 0.3-1.5% of the more soluble lead acetate introduced into the stomach was recovered beyond the gastrointestinal tract and liver, even after several days. Thus, there is a greater health risk, in general, from exposure to systemic poisons in the form of fine particles in inhaled air than from ingestion. However, the inhaled particles must be small enough to penetrate to and be deposited in the pulmonary air spaces. Furthermore, they must remain long enough so that they can dissolve and be transferred into the bloodstream. Particles deposited on the ciliated surfaces of the upper respiratory tract will be rapidly removed upward and swallowed; like the directly ingested material, they will produce systemic intoxication only in proportion to absorption from the gastrointestinal tract and transfer into the systemic circulation (Hatch and Gross 1964).

The particle size distribution of the inhaled material is of great importance: it will determine the quantity of particulate matter which is deposited in the lungs, and, for any given amount of deposit, it will determine the rate at which it will be transferred into the blood.

Wilson et al. (1948, 1952, 1955) showed dramatic differences in the amount of lung deposit from exposure to equal mass concentrations of uranium oxide dusts of two different particle sizes (0.5 and 2.5 µm). Ten times as much of the finer material was found in the lungs of animals killed 20 h after exposure. The ratio was considerably higher in animals kept for two or three months as a consequence of a more rapid clearance of the coarser particles from the lungs.

The differences in magnitude of the toxic (systemic) response from lung doses of particles made up of different sizes are of great interest. Presized fractions of uranium oxide from 10 down to 0.2 µm were introduced into rats by intratracheal injection, and the degree of resulting kidney damage and the amounts of uranium in bone and kidney were measured. Particles larger than 3 µm produced no demonstrable intoxication, but below this size the magnitude of response increased progressively as size decreased. It is probable that the fraction of material which escaped the rapid phase of clearance and remained in the pulmonary air spaces following the intratracheal injection was less for the larger particles, and, indeed, the fraction found in the lungs one week after dosing did decrease as size increased. Thus, the effective lung dose was undoubtedly higher for the finer particles (Hatch and Gross 1964).

The hazard presented by lead and other toxic materials is dependent on the chemical and physical form of the material. The small particle size increases solubility and, hence, rapid absorption from the lung (Dautrebande 1965). A study by Rendall et al. (1975) in which baboons were exposed to Pb_3O_4 showed that when the total lead dust cloud was considered, the larger particles of mass mean diameter 1.6 µm, which obviously represented greater quantities of lead, increased the lead level in blood considerably faster and to a greater extent than did the fine particles of mass mean diameter 0.8 µm. This was almost certainly due to different deposition patterns for the two particle sizes and hence different lung burdens, but indicates that larger particles should not be neglected.

4.8 ALLERGIC AND OTHER SENSITIVITY RESPONSES

The fact that particles of sensitizing capability are deposited either in the air passages or in the pulmonary air spaces does not, of necessity, localize a resulting allergic reaction to that site. The target tissue may be the mucous membrane of the paranasal sinuses, the conjunctivae, or even the gastrointestinal tract.

Air pollutants which are capable of initiating an allergic reaction include products of plant life such as pollens and fungi; industrially produced air pollutants such as nickel, chromium, and beryllium compounds; and synthetic organic compounds such as certain amines and plastics, particularly of the epoxy type, which are known to be sensitizers and which can cause allergic reactions when inhaled.

When the target tissue involved is the wall of the air passages, the allergic reaction is asthma, caused by spasm of the smooth muscle of the bronchi and bronchioles, and associated with edematous swelling of the mucous membrane of these structures. Involvement of the alveolar membrane in an allergic reaction takes the form of a granulomatous type of chronic interstitial pneumonitis, which is generally believed to be caused by the deposition of the specific inciting agent at, or very close to, the site of the inflammation upon the alveolar surface (Hatch and Gross 1964). Farmer's lung disease and bagassosis are two of the most frequently reported lung diseases in which the alveolar membrane is the target tissue of an allergic inflammation. In the former, the inciting agents are believed to be fungi growing on stored hay and straw. In the latter, the inciting agents are also believed to be fungi grown on bagasse, the residue of sugarcane following extraction of the sugar. Similar diseases have been described as being caused by the inhalation of dust derived from soil in which mushrooms had been grown and of dust consisting mostly of spores from a fungus associated with the bark of maple logs (Hatch and Gross 1964).

In byssinosis, a disease associated with the inhalation of cotton dust over a long period of time, the airway resistance is increased by constriction of the bronchioles. Constriction is a consequence of tissue response, presumably to locally deposited particles of organic substance from the cotton dust. Due to the location of response along the finer airways rather than in the pulmonary air spaces, it is assumed that particles of intermediate rather than of the finest size contribute most to the reaction (Roach and Schilling 1960).

4.9 AIRBORNE INFECTIONS

Settling velocity determines the duration of stay of infectious particles in air, and this, in turn, limits the probability of their transfer between persons sharing the same atmosphere (Hatch and Gross 1964). Thus, the risk of direct respiratory exchange of infectious particles is mainly restricted to the finer particles which may be dispersed from the respiratory tracts of infected persons, and the hazard from inhalation of particles resuspended from dust deposits will be limited by their relatively large size. Organisms are dispersed in liquid droplets by coughing, sneezing, and, to a lesser degree, talking. Droplet size varies from greater than 100 µm down to well below 10 µm, the mean size falling between 10 and 20 µm (Duguid 1946). It has been shown that, even with 90% relative humidity, droplets smaller than about 80 µm will evaporate before settling from a height of 2 m. The great bulk of these residual particles, which are called droplet nuclei, are only a few micrometres in size, having settling velocities of the order of 0.015-0.02 $cm.s^{-1}$. Such particles, some of which may contain virulent pathogens, are thus capable of remaining in atmospheric suspension over long periods of time and, during such times, can be inhaled by susceptible individuals sharing a confined atmosphere with infected persons. In order to establish disease, the particles must be deposited at the critical site (appropriate to the particular disease) within the respiratory system. A distinction may be made between large droplets, and dust-borne bacteria and fine droplet nuclei. The probability of pulmonary deposition is higher for droplet nuclei, whereas for dust-borne bacteria and droplets, deposition is essentially limited to the nasopharyngeal chamber and the upper part of the respiratory tract (Hatch and Gross 1964).

5.0 HEALTH EFFECTS OF INHALED PARTICLES

5.1 DEFINITION AND MEASUREMENT OF HEALTH EFFECTS

When studying the health effects of air pollution, we are usually concerned with variations in health indicators. The extent to which these health indicators differ from "normal" varies with what is socially and/or medically acceptable at any point in time. As new indices of health are developed, concepts change and new methods of measurement of biological response in humans result in a new set of norms defining health.

There is sometimes confusion between measures of exposure and response. Measures of exposure can be derived from ambient air measurements, measurements in a worker's breathing zone, or occasionally measurements of levels of contaminant (e.g. lead) in blood or other body tissues or fluids. In the case of inhaled particles, true dose to the organs is usually difficult or impossible to determine quantitatively, because particle removal, solubility, metabolism, and other body mechanisms are called into action once the particle has been deposited in the respiratory system.

Measuring response is equally complicated. Inhalation of particles may produce "signs" detectable by x-ray, whereas the person with such changes may not be aware of their existence. In some instances, such signs may be observed and not appear to be related to any functional disorders. On the other hand, symptoms may be reported by exposed persons in the absence of objective criteria to confirm their existence or evaluate their relevance. In studies of the effects of air pollution on health, measures of biological change (e.g. pulmonary function) in exposed persons may be considered as response. However, in some instances, the relationship between such changes and short-term or long-term health impairment may not be known.

Because of the complexities of defining specific health effects in the general population, the majority of information pertaining to the influence of particle size and shape on health has been derived from the study of occupational groups. In such circumstances, exposure levels have been well above those encountered by the general public, and exposed groups can be relatively well defined. However, extrapolation of the results of occupational studies to infer risks for the general population presents some difficulties. The work force is essentially a selected healthy segment of the general population, whereas the latter also includes babies, elderly persons, and persons with preexisting health problems. In addition, exposures are usually at a greatly reduced level.

A group of persons which is becoming increasingly important in understanding health effects of specific pollutants is the families of exposed workers. Persons living in the vicinity of well-defined industrial pollutant sources also have the potential to provide information on health effects related to exposure to specific agents.

5.2 EFFECTS OF AIR POLLUTION EXPOSURE

5.2.1 PARTICLE ACCUMULATION IN THE LUNG

One method of assessing exposure for studies of chronic health effects has been the measurement of particles in the lung at autopsy. Such methods can be useful in providing positive evidence of exposure, but the absence of particles from the lung does not preclude the possibility that exposure occurred. Studies of tissues obtained by biopsy or at autopsy can provide data on the form and sizes of particles retained in the lung. However, the interpretation of lung burden at death can be complicated by the preferential removal of certain materials from the lung, and it might be argued that materials responsible for a chronic health effect may have been removed when the health effect requires many years from onset to be detected.

Black pigmentation is a striking feature of the gross appearance of human lungs, as well as those of long-lived animals, at autopsy. Pearson (1813), apparently referring to the pleural surface, described mottling by the age of 65 or 70. He added that the condition of the interior of the lung, in great measure, corresponded to that of the surface, and concluded that the pigment was the result of deposits in the lungs from the dust and smoke in respired air. Zeidberg and Prindle (1963) suggested that the quantity of lung pigment might provide a useful index of exposure to air pollution. Pratt and Kilburn (1971) studied this pigmentation in 204 whole-lung sections (79 from nonsmokers and 125 from smokers) classified as "normal"[α]. The point-counting procedure of Dunnill (1962) was used. In nonsmokers, there was a slight correlation between age and pigmentation of the lungs, the rate of accumulation being 0.05% a^{-1}. The pigmentation was greater in smokers (6.7%) than in nonsmokers (2.6%); in city-dwelling smokers (7.4%) than in country-dwelling smokers (5.4%); and in blacks (6.6%) than in whites (4.8%). The index did not reflect small differences in the mean concentrations of airborne particles in two localities which were studied. Individual variations in pigmentation in smokers were large.

Lewis and Coughlin (1973) studied the content of acid-insoluble dust (soot) in 146 male lung samples obtained at autopsy. None of the subjects studied was suspected of having been exposed through occupation to coal dust, and persons came from two general hospitals situated in towns with low levels of air pollution. The mean soot

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[α] Normal in this case indicates absence of neoplasia, emphysema, and pulmonary fibrosis.

content of the 146 lung samples was 1.18 ± 0.10 $mg.g^{-1}$. The mean weight of both lungs was 1427 ± 41 g, and the mean total lung soot content of the subjects in this series was 1.7 ± 0.2 g. Older subjects had more lung soot than those in the younger age group. A statistically significant trend was found between age and quantity of soot accumulated. A linear regression analysis between age and soot content using the 146 observations yielded a slope of 0.0172 $g.a^{-1}$ of life. The mean lung soot content for blue-collar workers was not significantly different from that of white-collar workers. A significant difference in lung soot content was observed when nonsmoking, ex-smoking, and cigar- and pipe-smoking blue-collar workers were compared with cigarette-smoking blue-collar workers. However, no such difference was observed in white-collar workers. Inflammatory diseases, chronic bronchitis with or without emphysema, and acute pulmonary infection were not associated with any alteration in the lung soot burden, but the burden was higher in persons who died with cerebrovascular hemorrhage or thrombosis. The reasons were not clear. No information was made available on particle size.

5.2.2 TRACE ELEMENTS

Several studies (Koch et al. 1956; Tipton and Shafer 1964; Dixon et al. 1970; Keenan et al. 1971; Gibbs and Bogdanovic 1974) have been carried out to determine the total content of inorganic material in the lung and to measure the trace metals. Such studies do not show major differences in the trace metal content of lungs, except in the case of occupationally exposed persons. Unfortunately, such studies have provided no information on the size and shape of particles deposited or retained in different parts of the lung, because the specimens were generally analyzed chemically without microscopic examination. Other than observations of tissues for fibers, studies of particle size and shape in histological sections of lung from the general population do not appear to have been carried out.

5.2.3 FERRUGINOUS BODIES

It has long been recognized that asbestos fibers, when deposited in the lung, can become coated with an iron protein (see Section 4.3.3). These coated fibers can be stained with potassium ferrocyanide to produce a blue color, and are often observable under the optical microscope. Thomson et al. (1963) reported that 25% of lungs in 500 consecutive autopsies in Capetown, South Africa, contained "asbestos bodies". This raised the important questions as to how frequently asbestos fibers might be found in the lungs of individuals not known to be occupationally exposed, and as to the risk for these persons of asbestos-related diseases. This observation stimulated many studies of "asbestos bodies" in the lungs of urban dwellers in various parts of the world. The percentage of "asbestos bodies" found in the lung increased with the diligence of looking and improvements in techniques of identification (Table 5-1).

Table 5-1. Prevalence of ferruginous bodies in routine autopsy material (from Becklake 1976).

Location	No.[α]	Prevalence		Method	Year[β]
		%	Men/Women		
Perugia, Italy	109	1.0	1.5	Smears	1969
Schwerin, E. Germany	234	9.0	1.4		1971
Ann Arbor, USA	100	18.0	1.9		1969
Newcastle, England	311	20.3	2.4	Scrapings	1968
Glasgow, Scotland	100	23.0		Smears	1967
Jerusalem, Israel	100	26.0	1.3	Smears	1968
Cape Town, S. Africa	500	26.4	1.5	Smears	1963
Miami, USA	500	27.2	1.6	Smears	1966
London, England	394	36.8	1.4	Sections: left lower lobe	1975
Sarajevo, Yugoslavia	100	38.0	2.5	Smears	1971
Belfast, N. Ireland	200	40.5		Smears	1965
Pittsburg, USA	100	41.0	1.4	Smears	1965
Dresden, E. Germany	250	43.2		Smears	1967
Melbourne, Australia	200	43.5	1.0		1969
Johannesburg, S. Africa		47.0		Smears, scrapings	1965
Montreal, Canada	100	48.0	1.7	Scrapings	1966
Malmo, Sweden	97	48.4	1.4	Smears	1967
Milan, Italy	100	51.0	1.2		
New York, USA	100	53.0	1.2	Ashed sections	1934
"	100	60.0	1.0		1967
"	1,975	47.7	1.3	Smears	1966
London, England	127	0.0		Sections	1936
"	100	3.0	4.9	Sections	1946
"	100	14.0	1.3	Sections	1956
"	100	20.0	0.8	Sections	1966

[α] Number of autopsies in which a search for ferruginous bodies was made.

[β] Year of publication was usually within 1-2 years of the year in which the study was carried out. Note that for New York and London data at the end of the table, the actual year of the study is given.

In the late 1960s, Gross et al. (1969) coined a new term, "ferruginous bodies", to describe these coated fibers in the lung, as it was not known in all cases whether the core was asbestos or if other fibers such as glass could give rise to the same type of bodies.

Accurate identification of the cores is now possible using electron microanalytic techniques (Langer et al. 1971), but this is expensive and time-consuming. Studies of these cores have found that, in man, amphibole fibers are more frequently found in the cores of ferruginous bodies than are chrysotile fibers (Ashcroft and Heppleston 1973; Fondimare and Desbordes 1974), even when both types of fiber are found in the lung (Pooley 1973b; Churg and Warnock 1981). For members of the general population the core is almost invariably an amphibole; however, asbestos workers may have ferruginous bodies of either amphibole or chrysotile (Churg and Warnock 1981). Planteydt (1973) reported that it is probable that most of the ferruginous bodies found in the lungs of city dwellers contain asbestos.

The possible exposure of the general population to fibers raised the question as to whether or not there had been an increase in ferruginous body content as the commercial use of asbestos increased. Two studies were conducted using autopsy material to determine whether or not there had been such an increase. In the United States, Selikoff and Hammond (1970) found no increase in the quantity of ferruginous bodies in the lung between 1930 and 1960, whereas Oldham (1973) found an increase in the United Kingdom. Oldham also showed an urban-rural gradient, with higher prevalence in industrial and shipyard areas. More recently, it has been found that for every ferruginous body in the lung, there can be a substantially larger number of uncoated fibers, and in terms of assessing exposure of the general population to these fibers, this number is almost certainly more relevant. The ratio of coated to uncoated fibers is in the range of 10-30 to 1 (Ashcroft and Heppleston 1973; Fondimare and Desbordes 1974). While ferruginous bodies occur in higher concentrations in the lungs of occupationally exposed persons, where fibers in sputum can also be detected, ferruginous bodies in lung present some measure of the fiber (not necessarily asbestos) exposure of the general population.

5.2.4 FIBERS IN LUNG TISSUES

Gross et al. (1970) studied the presence of inorganic fibers and ferruginous bodies in the lungs of 27 city dwellers from Pittsburgh using optical microscopy. There were 12 males and 15 females in the study, and, except for one case (a 6-year-old girl), persons ranged in age from 35 to 89 years. Occupational histories were not obtained. The total dust content of the lungs of adults varied from 0.6 to 6.1% of their dry weight.

The estimated number of fibers ranged from 15,000 to nearly 400,000 per gram of dry lung in adults. A high amount (89,000 fibers per gram of dry lung) was found in the lungs of the 6-year-old girl. The estimated weight of the fibrous dust ranged from 0.01 to 1.4% of the total dust weight, but there was little relationship between the total dust content of the lungs and their fiber content. Most fibers were rectilinear, but a few curved ones were also present. The mean diameters of the fibers found in the lungs of adults ranged from 1.4 to 3.1 µm, and their mean length ranged from 16 to 38 µm. About 90% of the fibers were equal to or less than 3 µm in diameter. Between 48 and 85% of the fibers were 5-25 µm long; only 2-16% of the fibers were longer than 50 µm. In the child's lungs, the mean diameter of fibers was 1.5 µm, and the mean length was 14 µm; the majority of fibers had a diameter of 1 µm and a length of 5-10 µm.

Ferruginous bodies were found in all lung residues, their number ranging from 28 (in the residue of the child's lung) to 4000 per gram of dry lung. The number of ferruginous bodies per milligram of dust in the lung ranged from 6 to 450. There was no relationship between the dust content of the lung and the number of ferruginous bodies found, nor between the number of ferruginous bodies and that of uncoated fibers present in the lungs. Diatom fragments and occasional intact small diatoms were found in nearly all deposits in adult lungs. Another type of inhaled foreign material found in many lung residues consisted of carbonaceous remnants of burned paper and plant tissues. The different shapes and sizes of the fibers found in the lungs of city dwellers were considered suggestive of their multiple origins. The distributional peaks of fiber diameters and lengths derived from the ash of tissue paper and classified according to size coincided with the peaks of the distribution of fibers derived from the lungs of adult city dwellers. The authors concluded that a detailed analysis of fibers is required before reaching conclusions as to the types of fiber in human lung.

Studies of fibers in lung tissue require careful scrutiny. The study by Gross et al. (1970) was restricted to optical microscopic observations, and narrow (<0.21 µm) fibers would not have been seen. Tissue preparation and storage also require attention. In one study (Gibbs 1982) it was shown that many fibers similar in form to asbestos which were found in a lung were actually potassium oxalate crystals; the lung had been stored in such a solution by the pathologist. Specimens may also be contaminated by fibers from water used to prepare solutions for specimen preservation.

By the mid-1970s, the importance of electron microscopic observations was widely recognized. In a study of 28 consecutive urban dwellers examined at autopsy in New York City, chrysotile was identified by electron microscopy in the lung tissues of 24 cases (Langer et al. 1971). Using both optical and electron microscopic methods, Gross et al. (1974a) studied at autopsy the lungs of 30 persons for the presence of fibers. There was wide variation in the concentrations of optically and electron microscopically visible mineral fibers, mineral dust fibers shorter than 5 µm, and fibers identifiable as chrysotile in the lung. The concentrations of optically visible fibers ranged from 400 to

170,000, with an average of about 25,000 fibers, per gram of dry lung. The concentrations of such fibers in the lungs of persons with pathological signs of asbestosis averaged 4 million per gram of dry lung. The percentage of mineral fibers identifiable as chrysotile was 7%, whereas in asbestotic lungs of chrysotile-exposed persons it approached 95%. The concentration of electron microscopic sized fibers in lung tissue ranged from 100 to over 1000 times that of optically visible fibers; 54-85% of these fibers were less than 5 µm in length. There was no relationship between the number of fibers and the concentration of mineral dust in the lung. Differences were found between persons from Pittsburg and those from Charleston; the mineral dust content was 9.5 $mg.g^{-1}$ in the former and 2.8 $mg.g^{-1}$ in the latter, while the numbers of fibers were 45.2×10^3 and 6.5×10^3, respectively. These differences probably reflected the different levels of air pollution in the two towns, Pittsburg being highly industrialized, and Charleston being a relatively clean seacoast locality.

Although restricted to optical observations, some information on dust in the lungs of asbestos industrial workers and its relation to disease was reported by Beattie and Knox (1961). The amount of mineral matter in the lungs appeared to increase with exposure time, but did not correlate with the degree of asbestosis. The asbestos material within the lung tissue was studied to determine if there was any significant difference between the numbers of particles of different size ranges in the various lobes and those in different parts of the lobes. It was found that in any one lung the proportion of fibers in different size ranges was uniform. Samples taken from different parts of both lungs were therefore pooled. In every specimen studied, the particles in the lowest size range (i.e. <5 µm) exceeded 50% of the total light optical count. In the five cases who did not survive for more than six months after the last exposure to asbestos dust and who died in the years 1955-1958, there were no large optically visible fibers present in the over-45-µm range. There were six cases who died between 1950 and 1953 and who survived less than 1 year after last exposure to asbestos dust; four of these cases had appreciable numbers of long fibers in the over-45-µm range. There was an appreciable diminution of fibers in the 23- to 35-µm and 36- to 45-µm ranges in the cases who died between 1955 and 1958 as compared with those who died between 1950 and 1953. These findings suggested that sometime after 1953, fewer long fibers were present in the airborne dust in factories.

When the survival time exceeded 8 years, fibers longer than 45 µm had fragmented or were rarely detected. After 13 years, no fibers with a length in excess of 36 µm were present. When asbestosis developed, there appeared to be a downward trend in the number of particles in the large size ranges. Unfortunately, these studies did not involve electron microscopic examination of the fibers, but the results (although the exposures were not well known) do suggest that optically visible chrysotile fibers disappear from the lung with time since last exposure. Whether electron microscopically visible fibers also disappear is not known, and a study of Quebec chrysotile miners is now under way to examine this question of fiber retention (Rowlands et al. 1980).

In a study in France, Sebastien et al. (1977) analyzed asbestos fiber concentrations in the lungs of three groups using both optical and electron microscopic methods. The study groups were six asbestos workers with histories of heavy exposure to asbestos (group 1) and six subjects who had handled small amounts of asbestos during their professional lives (group 2) (one case showed mild fibrosis). The third group served as a control and consisted of six randomly chosen cases from a series of 50 cases autopsied where there was no known asbestos exposure history.

Light optical counts showed a major difference in the lung content of fibers between groups 1 and 2 (Table 5-2). However, the proportion of optically visible fibers fell from 10% in group 1 (range 4-20%) to 0.21% (range 0.05-0.50%) in group 2. This shows clearly that electron microscopy is essential for assessing fiber exposures using measurements in tissue. Chrysotile fibers were found in bundles as well as being present in fibrils, but the latter outnumbered the former. Use of the electron microscope microprobe analyzer for quantitation of particles in biological tissue is described by Henderson (1975).

While there have been recent interlaboratory comparisons of analyses which suggest that agreement can be reasonably close, there have been many different analytical techniques applied, and the methods of expressing the fiber content of lung tissues have made comparisons of the results from various studies extremely difficult. Some standardization in reporting of techniques and additional interlaboratory evaluations might be valuable.

Additional information on the fiber content of tissues is described in Section 5.4 where it is discussed in relation to specific health effects.

5.3 HEALTH EFFECTS OF AIR POLLUTION

Although high concentrations of ambient air pollutants have been shown to increase mortality and exacerbate preexisting diseases, the studies performed to date provide no information on the importance of various particle sizes or shapes in producing health effects. Indeed, much of the effort in population studies has been directed towards demonstrating relationships between the total airborne concentrations of particles and other air contaminants and chronic bronchitis, lung cancer, emphysema, and pulmonary function abnormalities.

The health effects of particulate pollution have been reviewed by Holland et al. (1979). They concluded that mortality in adults was increased by short-term exposure to high concentrations of air pollutants. This conclusion was based on observations during high

Table 5-2. Optical observations of fiber concentrations in lung tissues (from Sebastien _et al_. 1977).

Method	No. of fibers per cm^3 Group 1	Group 2	Group 3
Light optical	2×10^6	2×10^3	2×10^2
Electron microscope	1×10^7	1×10^6	

pollution episodes in London between 1952 and 1967, when average daily smoke concentrations were equivalent to total suspended particulate (high volume) concentrations of 600-800 $\mu g.m^{-3}$. As far as long-term exposures were concerned, the authors found that "there is no scientifically acceptable evidence from recent mortality studies of long-term exposure to air pollution that can implicate a particular level at which an increase in deaths can be identified". They also concluded that there was good evidence showing lack of effect on health in the range 80-130 $\mu g.m^{-3}$ of total suspended particulates as an annual geometric mean. For persons with chronic bronchitis, increased illness was found when the 24-h average concentration of total particulates exceeded about 350 $\mu g.m^{-3}$ with a SO_2 concentration of 500 $\mu g.m^{-3}$. In children, definite effects of air pollution on health occurred when total suspended particulate concentrations were at and above 330 $\mu g.m^{-3}$ in the presence of SO_2 at concentrations of about 180 $\mu g.m^{-3}$ (annual means). There was no evidence of effects at or below 240 $\mu g.m^{-3}$ in the presence of SO_2 levels of about 180 $\mu g.m^{-3}$ as annual means.

A recent document (EPA 1981) has reviewed the investigations of effects of both acute and chronic exposure to sulfur oxides and particulate matter (see Tables 5-3 and 5-4, respectively).

In all cases where relatively reliable studies have been conducted, gaseous pollutants have also existed. This demonstrates one of the difficulties of considering general particulate pollution in the absence of other air pollutants, and suggests that future studies should be directed at specific pollutants of defined characteristics and specific health effects rather than at general health effects. At current levels of total particulate air pollution in most Canadian cities, it is unlikely that studies of the relationships between currently accepted measures of health and total particulate pollution will provide any conclusive positive evidence of health effects related to air pollution.

5.3.1 GENERAL MORTALITY

Studies of mortality dealing with the immediate effects of air pollution can be carried out only in large populations. During the great London fog of December 1952, when a population of eight million people was subjected to extremely high levels of pollution, the total additional (excess) number of deaths associated with the episode was estimated at 4,000. The excess death rate per 100,000 population per day of fog was 12.2. Daily variations in the level of air pollution have been shown to be associated with comparatively small variations in the number of deaths. In this and the later 1964 smog, the increased mortality was related to increased smoke and sulfur dioxide concentrations (see Figure 5-1). Other acute pollution episodes widely accepted as resulting in increased mortality include those in the Meuse Valley (Firket 1931), Donora (Schrenk *et al.* 1949), New York City (Greenburg *et al.* 1962a,b), and Osaka (Watanabe 1965).

Table 5-3. Summary of quantitative conclusions from epidemiological studies relating health effects of acute exposure to SO_2 and particulate matter to ambient air levels (from EPA 1981).

Type of study	Effects studied	24-h average pollutant level ($\mu g.m^{-3}$)			Reference
		Particulate matter[α]			
		BS	TSP	SO_2	
Mortality	Likely increases in daily total mortality above a 15-d moving average during winter 1958-1959 among persons with existing respiratory or cardiac disease in London	> 1000	-		Martin and Bradley 1960
	Slight indication of likely increases in daily total mortality above a 15-d moving average during winters of 1958-1959 and 1959-1960 among persons with existing respiratory or cardiac disease in London	750-1000	-	710-1000	Martin 1964
Morbidity	Likely worsening of health status among a group of chronic bronchitis patients	250-500	-	500-600	Lawther 1958; Lawther *et al*. 1970
	No apparent response or worsening of health status among a group of chronic bronchitis patients	<250	-	<500	Lawther *et al*. 1962, 1970

[α] BS, smoke; TSP, total suspended particulates.

Table 5-4. Summary of quantitative conclusions from epidemiological studies relating health effects of chronic exposure to SO_2 and particulate matter to ambient air levels (from EPA 1981).

Type of study	Effects studied	Annual average pollutant level ($\mu g.m^{-3}$)			Reference
		Particulate matter[α]			
		BS	TSP	SO_2	
Cross-sectional (4 areas)	Greater prevalence of cough and phlegm in areas of elevated BS and SO_2 pollution, observed in survey of 10,000 British postal workers	100-200+	-	150-200+	Lambert and Reid 197
Cross-sectional (4 areas)	Likely increased frequency of lower respiratory symptoms and decreased lung function in children	230-301	-	181-275	Lunn *et al*. 1967
Cross-sectional (4 areas)	No observed effect on respiratory symptoms and lung function in children	48-169	-	94-253	Lunn *et al*. 1970
Longitudinal and cross-sectional	Apparent improvement in lung function of adults in association with decreased particulate matter pollution in Berlin, N.H.	-	180	-	Ferris *et al*. 1973, 1976
Longitudinal and cross-sectional	Apparent lack of effects and symptoms, and no apparent decrease in lung function in adults	-	80-131	-	Ferris *et al*. 1973, 1976
Cross-sectional (5 cities)	No apparent evidence of increased symptom prevalence or chest illness among telephone plant workers	-	70-163	-	Holland and Stone 1965; Deane *et al*. 1965; Comstock *et al*. 1973

[α] BS, smoke; TSP, total suspended particulates.

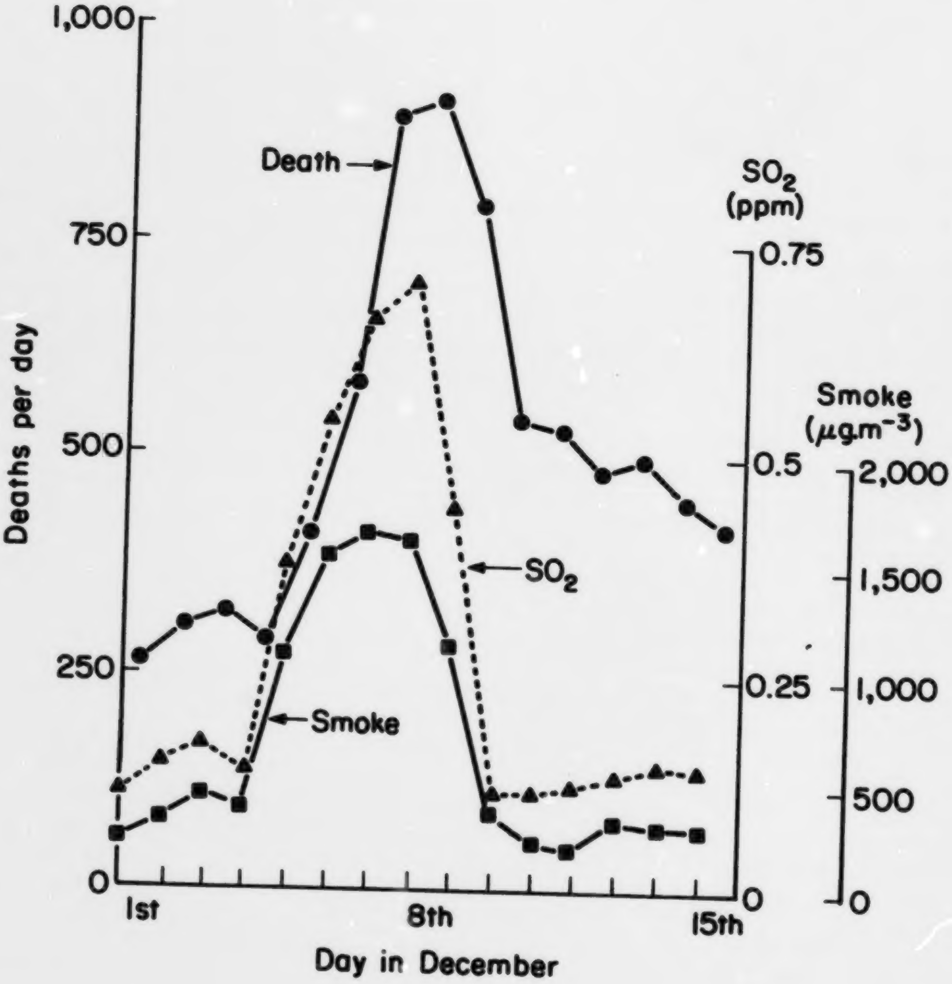

Figure 5-1. Air pollutant levels and excess mortality in London in December 1952 (from Bates 1972).

In smaller populations, the acute effects of air pollution on mortality will be difficult to assess; only rarely will incidents associated with an increased level of air pollution produce a statistically significant rise in the number of deaths, and under such circumstances a long series of observations would be needed to demonstrate any association between the two.

5.3.2 RESPIRATORY CANCER

An example of a specific disease which has been studied for its association with particle exposure is lung cancer. The causal association between cigarette smoking and lung cancer has been well established (Advisory Committee to the Surgeon General 1964), but the active carcinogenic agents responsible for the effects of smoking in man are still not known. There are also a number of occupational particle exposure situations which have been shown to be associated with increased risks of lung cancer. These include exposure to radon daughters in uranium mining (Archer et al. 1973), exposure to chromates (Mancuso 1951), exposure to asbestos (Becklake 1976), employment on coke ovens (Lloyd 1971), and exposure to "tars" in aluminum reduction plants (Gibbs and Horowitz 1979), as well as in a number of other occupations. In the occupational setting, it has sometimes been possible to demonstrate dose-response relationships between indices of exposure and lung cancer mortality. However, even in the occupational environment, data on levels as well as physical, chemical, and mineralogical characteristics of contaminants in the work place have usually been inadequate to determine whether particles of certain sizes or even specific materials are implicated in the production of health effects.

Factors such as smoking habits and other airborne contaminants (as exposures are rarely to a single substance) have complicated the interpretation of the results of even the most carefully planned and executed epidemiological studies. It is therefore hardly surprising to find that studies of the general population are even more difficult to interpret. The epidemiological evidence for associations between particulate air pollution and cancer mortality has been well reviewed (Cederlof et al. 1978; U.S. NRC 1979). It is clear that cancer mortality is higher in urban centers than in rural areas in many countries. However, the differences in autopsy rates, diagnostic biases, smoking habits, diet, and occupations between urban and rural districts make it difficult if not impossible to determine the contribution made by air pollution to the mortality differences.

The role of fibers in the production of the specific tumor mesothelioma and other cancers is discussed in Section 5.4.2.2.

5.3.3 ACUTE MORBIDITY

The study of sickness records might be expected to be more fruitful than investigations of mortality, since morbidity is a more sensitive indicator of deviation from normal health and well-being. Such studies should show the effects of air pollution on the normal population and not only on those already suffering from some severe disease. Data on morbidity can be derived from several sources.

(i) Hospital admissions - The daily number of applications for admission to hospitals can provide a useful index of morbidity associated with air pollution. By its nature, this indicator can reflect only the more severe illness, since trivial cases are not usually admitted to hospitals. As with the daily numbers of deaths, the figures concerning hospital admissions are relatively small, and the method is therefore likely to be used only in dealing with large populations. One such study was that of New Orleans asthma in which large increases in asthma admissions occurred within 24-h periods. This study showed that the epidemic of asthma was related to sensitization to natural inhalant allergens acting in seasonal patterns (Salvaggio et al. 1971).

(ii) Medical certificates - Certificates issued by doctors to enable patients to collect benefits under insurance or social welfare schemes have also provided information that can be used in determining the immediate health effects of high levels of air pollution. Attention must be paid to variations in the number of persons asking for a medical certificate due to factors such as holidays, seasons, or day of the week.

(iii) Work absenteeism - Absenteeism from work for health reasons (whether medically certified or not) has been used as another indicator of health effects of air pollution. It has, to a certain degree, the same limitations as the rise in issuance of medical certificates, in addition to other problems such as dissatisfaction with work and industrial environmental problems. Absenteeism relates to the healthiest group of the population, the very young, the very old, and many of the chronically ill being excluded.

(iv) Morbidity in children - Measurement of morbidity in children is believed by many investigators to provide a suitable indicator for assessing the health effects of air pollution (Kerrebijn and Mourmans 1975). The studies carried out so far have mostly been concerned with the long-term effects of air pollution.

(v) Morbidity in the aged - Because of their greater susceptibility to environmental factors, elderly people are also considered a useful group for studying the health effects of air pollution.

(vi) Studies on patients with chronic diseases - The effects of acute episodes of high levels of air pollution are most evident in patients suffering from chronic heart or lung disease. A method of demonstrating the effects of varying degrees of air pollution on patients suffering from chronic bronchitis was developed by Lawther (1958). Patients attending hospital clinics were asked to keep personal diaries in which each recorded his own assessment of his daily condition ("*better*", "*same*", *or* "*worse*", compared with the day before). From numerical translations of the diary entries, it was possible to construct trend lines showing the day-to-day condition of the group as a whole. Analysis of the results indicated that the patients were not influenced by their knowledge of the weather at the time. The results demonstrated this method of study to be one of the most sensitive ones presently available. It is independent of any form of mortality or morbidity registration and is suitable for use in relatively small communities.

Apart from a few isolated incidents elsewhere (e.g. Meuse Valley, Donora), only in the United Kingdom has it been possible to demonstrate the immediate effects of changes in air pollution. Daily values of the concentration of black suspended matter and sulfur dioxide have been correlated with indices of mortality and morbidity, and have shown a much closer association than was previously suspected. The effects that are noticeable in patients suffering from cardiac or respiratory conditions may be observed within a few hours of a deterioration in atmospheric conditions, and are frequently evident even with quite small increases of pollution. The peaks in mortality are often followed by a corresponding fall, suggesting that the rise in air pollution may have determined only the time of death in patients who would otherwise have died during the next 24-48 h. These effects of air pollution have been noted only during the winter, and with the onset of spring this association with sickness and death disappeared.

5.3.4 CHRONIC MORBIDITY

The significance of less severe acute episodes and continuous exposure to increased levels of air pollution is still controversial. In children, some investigations found a positive relationship (Toyama 1964; Girsh et al. 1967; Lunn et al. 1967; Holland et al. 1969; Shy et al. 1970, 1973), whereas others found no such relationship (McMillan 1969; Biersteker and van Leeuwen 1970). Still others found only a partial relationship (Anderson and Larson 1966; Ferris 1970; Colley and Reid 1970).

Typical of the types of indices of health used are those adopted by Czechoslovakia, Denmark, the Netherlands, Poland, and Romania in field studies of between 3,000 and 5,000 school children (Kumpf et al. 1975; Arhirii et al. 1976). Questionnaires on respiratory symptoms were answered by parents and correlated with lung function tests.

The advantage of studying the influence of air pollution in children is that the respiratory tract in childhood is possibly sensitive to environmental hazards and cigarette smoking. Occupations have not yet come into play, although there are data to suggest that passive smoking might be important. Such studies have provided no information on the role of particle size and shape, although a study has been proposed to investigate the pulmonary function of children at various distances from industrial sources of pollution on the assumption (to be backed by measurements) that particle size will change with distance (Pengelly 1979). While such a study would be of great interest, it is not yet clear whether existing tests of pulmonary function would detect changes at the measured concentrations, or how variations in the socioeconomic status of children at various distances from industrial sources of pollution and changes in pollution quality can adequately be taken into account. Studies in the Montreal region have shown that the only pulmonary function test which distinguished children living in high- and low-polluted areas was the closing volume test, and the implications of such changes in terms of long-term effects is not known (Becklake et al. 1978).

The results of several studies have shown the combined effect of particulate and sulfur dioxide exposures on health outcome. These are summarized in Figure 5-2, which indicates a clear dose-response relationship between health effects and particles and sulfur dioxide. This figure indicates that at the levels of particles encountered in most communities in Canada today (levels for three regions near Montreal are shown), the nonspecific health effects are likely to be slight. It is this problem which precludes the likelihood of demonstrating any improvement in the relationships between effects on health and air pollutants by selecting size fractions of particles for study, unless a specific effect is anticipated.

5.4 HEALTH EFFECTS OF FIBROUS PARTICLES

Although studies of total particulates have provided little information on the relationships between particle size and health effects, there are two responses associated with exposure to asbestos fibers which have been found in general populations: (i) calcification of the pleura; and (ii) primary malignant mesothelioma.

5.4.1 PLEURAL CALCIFICATION

Localized areas of pleural thickening which become radio-opaque through calcification have been recognized for at least 250 years. Early reports (Ulrich 1930; Head 1934; Kristiansen 1939; Floyd and Hepburn 1944) focused on their possible association with tuberculosis, chest wounds, emphysema, hemothorax, pleurisy, and artificial pneumothorax. Siegel et al. (1943) suggested pleural occupational exposure as a factor in pleural calcification in tremolite

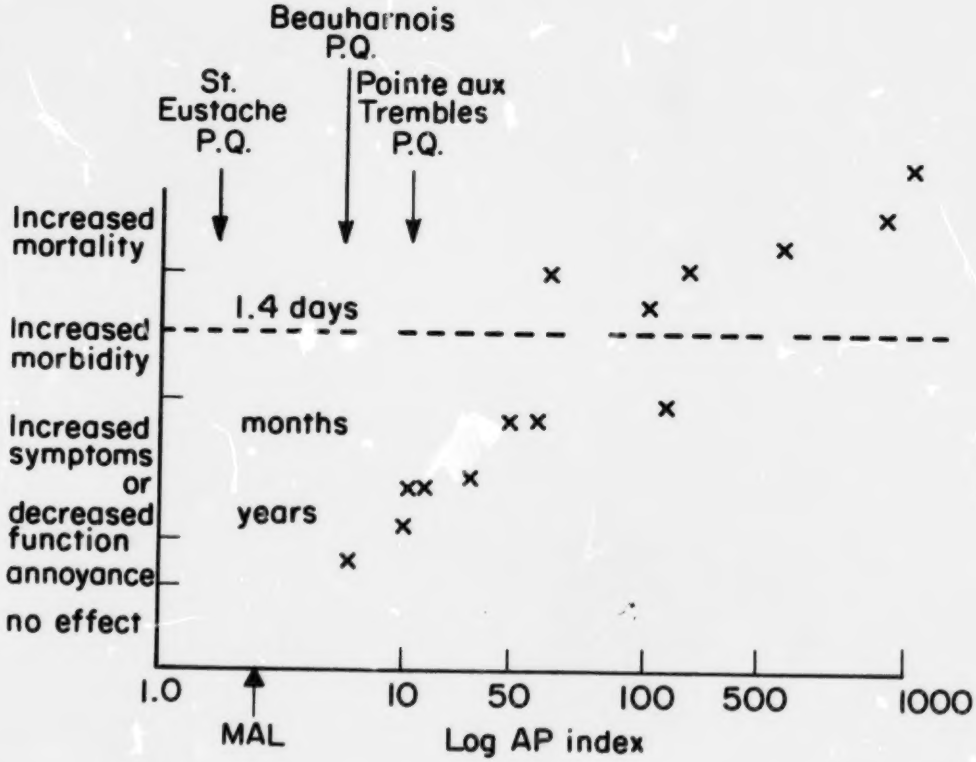

Figure 5-2. Dose-response curve for total suspended particulates. MAL = maximum allowable limit; air pollutant (AP) index = (SO_2) (suspended particulates)/1000 ($\mu g.m^{-3}$)^2 (from Becklake *et al*. 1976, based on data provided by Ferris 1975).

talc miners and millers in New York State. Smith (1952) reported on the frequency of pleural calcification in persons exposed to various dusts, indicating slightly higher crude frequencies of calcification in workers exposed to bakelite, calcimine, mica, and tremolite talc dusts. By 1960, certain occupational groups exposed to asbestos had been shown to have calcified pleural plaques as a relatively common radiological finding (Frost et al. 1956), particularly among older employees. Calcified plaques were also described in persons living near environmental sources of asbestos (Kiviluoto 1960). Physiological studies have not revealed any important loss of pulmonary function in persons with calcified pleural plaques (Leathart 1968; Becklake et al. 1972).

In 1959, primary malignant mesothelial tumors of the pleura were recognized in persons exposed to crocidolite asbestos (Wagner et al. 1960). This association between malignant mesothelioma and asbestos exposure was subsequently confirmed by other investigators, and speculation that the two pleural reactions (mesothelioma and calcification) might be related prompted renewed interest in the occurrence of calcified pleural plaques (Selikoff 1965; Raunio 1966; Burlikov and Michailova 1970; Navratil 1971). Reports have also shown that there are wide variations in frequency between geographical regions. Some of the rates, based on screening large populations, have been 0.15% in Denmark (Kristiansen 1944), 0.05-9% in Finland (Kiviluoto 1965; Raunio 1966), 0.066-4.5% in Bulgaria (Zolov et al. 1967), 1.8% in one region of Russia (Ginzburg et al. 1970), 0.1-6.6% in Czechoslovakia (Rous and Studeny 1970), and 0.023% in Leipzig, Germany (Neef 1963). In a study of inhabitants of a village situated in the vicinity of an asbestos plant in Czechoslovakia, pleural calcification was more common among blood relatives of cases than in other inhabitants (Navratil 1971). There was some evidence of familial aggregation in a recent Quebec study (Gibbs 1979), but this could well have been due to a common environmental exposure.

In Finland, anthophyllite fibers were considered to be the cause of pleural calcification, but talc was also mined there (Kiviluoto 1965; Meurman 1966). Burlikov and Michailova (1970) suggested that sepiolite fibers present in concentrations up to 5% in soils in certain areas might be responsible for pleural calcification in Bulgaria. In villages and towns around Diyarbakir in southeast Turkey, where walls of houses have been painted with chrysotile asbestos, pleural calcification rates ranged up to 14% (Yazicioglu 1976). However, more complete information on the materials used is required.

Etiological agents and factors have been sought to explain the experience of chrysotile asbestos miners and millers in Quebec (Gibbs 1979). Pleural calcification was identified (radiologically) in 198 men who had worked in the Thetford Mines area, six at Asbestos and two at St-Remi de Tingwick, representing rates of 2.5, 0.08, and 1% of the workers from these areas, respectively. Chrysotile asbestos is mined in each of the areas, and even when levels of exposure were taken into account, they did not explain the difference in pleural calcification rates. More detailed study of the distribution of cases by occupation showed that pleural calcification in Thetford was restricted to persons having worked mainly in one small group of mines, and was more common among miners than millers. This suggests that exposure to some materials in the mining operation was responsible for the calcification, and that this risk factor was not so common in milling. Calcification was not related to past history of injury, place of residence, or employment in other industries. To date, the only minerals which distinguish the mines with different rates are mica, talc, and breunnerite, which occur at the borders of the deposit in which the calcification rates are high. The finding of tremolite in the lungs of chrysotile miners shows that the potential for exposure to other fibers and materials exists (Pooley 1976; Rowlands et al. 1980). Thus, these exposures as well as differences in the nature of the chrysotile fiber in this mining region cannot be ruled out.

Although the etiological factors in pleural calcification remain unknown, there is evidence that it is associated closely with asbestos exposure. Because of the complexity of the geology of the various areas of the world where pleural calcification rates are elevated, the identification of a common factor without a thorough knowledge of the geology or mineralogy of these areas is almost impossible. Although fibers have been found in calcified plaques, there have been no systematic studies to compare the compositions of fibers or particles in the lungs or on the pleura of persons of similar circumstances but with and without calcification of the pleura, or in-depth studies of fiber sizes. Such studies might provide clues to etiology, but are subject to the difficulty that pleural calcification occurs a long time after first exposure. The evidence suggests that fibers or associated minerals are responsible. At the present time, the frequency or regional distribution of pleural calcification among the general population in Canada is not known.

The distribution of mesothelioma and pleural calcification in the main asbestos mining areas of Quebec is such that it is unlikely that there is a direct link between them. Additional evidence for this lack of association exists in Finland, where primary malignant mesothelial tumors have not been reported, and yet the rates of pleural calcification are high. There are technical difficulties in studying the link between localized uncalcified pleural thickening and the occurrence of pleural mesothelioma. One such study in the United Kingdom found an association between pleural plaques and mesothelioma; however, in interpreting these results, the author (Fletcher 1972) failed to consider that in order to have pleural plaques the asbestos workers must be in a certain age group and must have been first exposed much earlier, and that on reading an x-ray it might be difficult to distinguish the early stages of a malignant mesothelioma from pleural plaques. A further study by Edge (1979), in which men with and without pleural plaques were followed up, showed them to have a twofold risk of dying from lung cancer compared with that of the general population. However, Edge suggested that continued follow-up of the men is needed because of the long latent period before any final conclusion is reached.

5.4.2 MALIGNANT MESOTHELIOMA

The more important health effect from the standpoint of the public and public concern which has been linked with exposure to asbestos is malignant mesothelioma. In 1959 it was noted that certain patients with a diagnosis of pleural tuberculosis in hospital at Kimberley, South Africa, were not responding to antituberculosis therapy. Close examination of the cases led to the recognition of what had been an extremely rare tumor, the primary malignant mesothelioma tumor of the pleura and peritoneum (Wagner et al. 1960). Affected persons had lived or worked in the crocidolite asbestos mining area of Cape Province, and by 1968 more than 100 cases had been found in this area (Webster 1973). Only three cases were reported from the Transvaal where amosite is mined, and none from the South African chrysotile mines. Since 1960, a large number of epidemiological studies have provided further evidence of an association between asbestos exposure and primary malignant mesothelial tumors. A thorough review of the epidemiology of mesothelioma was reported by McDonald and McDonald (1977). Between 1959 and 1976, 4,539 fatal cases of malignant mesothelial tumors were reported from 22 countries. Proportional mortality rates ranged from 5.2 to 8.8% in insulation workers, 0.8 to 6.9% in asbestos factory workers, and 0 to 0.9% in anthophyllite and chrysotile miners and millers, compared with 0.03 to 0.06% in general populations. These authors concluded they could not calculate the rates for crocidolite, but most cases in production workers were associated with that fiber type. Additional support for the fact that crocidolite is more likely to produce mesothelial tumors than the other varieties of asbestos is found in the high occurrence of mesothelioma among crocidolite gas mask workers (using Australian crocidolite) employed during the last World War both in the U.K. (Jones et al. 1976) and in Canada (McDonald and McDonald 1978). Further support comes from the observations of 30 cases of pleural mesothelioma in 6,200 men employed in the Australian crocidolite mines between 1943 and 1966 (Hobbs et al. 1980).

The major increase in risk of mesothelioma appears to be occupationally related. No cases of mesothelioma have been reported among anthophyllite miners, and the rates appear to be considerably lower for chrysotile miners and millers (McDonald et al. 1974) than for insulation workers (Selikoff et al. 1973) or factory workers (Newhouse and Thompson 1965). Although there is a suggestion of a gradient from crocidolite through amosite to chrysotile and anthophyllite, adequate data on levels of industrial exposure are not available, and the special hazards of insulation and shipyard workers are not yet fully explained. In experimental animals it has been possible to produce mesothelioma by injection onto the pleura of all varieties of asbestos, and, more recently, to produce mesothelioma using fibers other than asbestos.

There is also some experimental evidence that the diameter and length of fiber are important for the production of this tumor. Pooley and Clark (1979) examined autopsy lung tissue from mesothelioma patients and found that the size characteristics of the three fiber types examined - chrysotile, amosite, and crocidolite - were very different. For chrysotile, the aspect ratio increased by a factor of approximately 40 with a 20-fold increase in fiber length. However, for amosite and crocidolite, the mean width of fibers increased in proportion to increasing length. The chrysotile fibers found were on the average the shortest fibers with finest diameters, whereas the amosite fibers were the longest with coarsest diameters. Crocidolite fibers were intermediate in size. Studies in Canada examining the dimensions of airborne fibers in various industrial operations to determine whether or not the sizes of fibers (i.e. length, diameter, aspect ratio, and shape factors) explain the apparent differences in mesothelioma rate in different occupational groups show that airborne fibers of different types vary markedly in their size distributions (Gibbs and Hwang 1975, 1980; Hwang 1981; Hwang and Gibbs 1981). While fiber dimensions change somewhat with processing, these changes are less than interfiber type differences. South African Cape crocidolite has a higher aspect ratio than amosite and Canadian chrysotile (Hwang 1981).

An observation by Baris et al. (1978) is particularly relevant to the study of mesothelioma. A high incidence of malignant mesothelioma has been reported in one community (Karain) in Turkey. Among 575 inhabitants, there were 11 deaths from pleural mesothelioma in 1975-1976. In the previous 5 years, 25 cases of mesothelioma had occurred. In this area, the fibrous zeolite (erionite) occurs, and this and other fibers are currently under investigation as possible etiological factors. If these prove to be responsible for this local high incidence of tumors, it would seem important that attention be paid to other regions where other fine fibers are used or might naturally occur. Complete data on the dimensions of fibers from that area are not yet available, although erionite fibers are of fine diameter (Pooley 1979; Hung et al. 1979) (see Table 5-5). Wagner (1982) has very recently shown that very fine erionite fibers are extremely carcinogenic when in contact with the pleura of experimental animals. Thus it is now very evident that dimensions of fibers are a critical factor in mesothelioma production in both man and animals.

5.4.2.1 Mesothelioma in Canada

The mortality of Quebec chrysotile miners and millers has been well studied. In a cohort of 11,488 persons born between 1891 and 1920, 1,457 of these had died as of November 1, 1966. At that time, three malignant mesothelioma tumors were found in that population. In a follow-up of the same cohort describing the mortality to 1969, 3,270 had died, and five mesotheliomas had been found (McDonald et al. 1974). By the end of 1978, 18 cases had occurred in this cohort (McDonald 1979a). The studies demonstrated an excess risk of mesothelioma for chrysotile

Table 5-5. Some man-made and naturally occurring fibers as seen by optical and transmission electron microscopy (from Hung *et al*. 1979).

Material	Diameters	Largest observed lengths	Comments
Sepiolite	< 0.5 µm	up to 10 µm	Fibrous nature difficult to observe by optical microscopy
Mordenite	< 0.5 µm	< 1 µm	Fibers not seen by optical microscopy
Chabazite	~1 µm	< 5 µm	Laths or cleavage fragments rather than fibers
Halloysite	< 0.5 µm	< 5 µm	Not well-defined fibers; probably cleavage fragments; not visible by optical microscopy
Erionite	< 0.5 µm	up to 50 µm	Fibrous
Attapulgite	< 0.2 µm	up to 0.5 µm	Fibers not visible by optical microscopy
Wollastonite	< 0.5 µm	up to 40 µm	Lathlike optically, more fibrous electron microscopically
Gypsum	< 1 µm	up to 20 µm	Aggregates and fibers
Nemalite	< 1 µm	up to 30 µm	Well-defined fibers
Carbon	~5 µm	up to 10 µm	Chunky fibers
Mineral wool	0.5-2 µm	> 100 µm	Well-defined fibers
Alumina-silica	~1 µm	40 µm	

Note: Large variations in the dimensions of naturally occurring fibers are possible, and these measurements reflect only a very limited cross section.

miners and millers, but the risks for the employees in this industry were considerably less than those which have been described for other industrial operations such as insulation work. There has been no report of mesothelioma among workers from the other chrysotile mines and mills in Canada. Crocidolite and amosite are not mined in Canada, although some deposits of crocidolite are recognized, and mineral contaminants similar in composition to amosite occur.

The occurrence of fatal malignant mesothelial tumors in Canada between 1958 and mid-1968 was ascertained by McDonald et al. (1970), who registered all fatal mesothelial tumors known to pathologists in Canada. These totalled 165 (1 per million population per annum). Two-thirds of these mesothelial tumors were in males. By comparing the cases with two control groups consisting of a secondary lung cancer and a primary lung cancer from the same hospital, matched as closely as possible for age and date of death, these authors showed an association between mesothelial tumors and definite or probable occupational exposure to asbestos, although only 20% of male cases and 1 female case had any such exposure. Almost all the excess of mesothelial tumors was among persons engaged in manufacturing and industrial application of asbestos rather than mining and milling, suggesting either that chrysotile is less associated with mesothelial tumors than are other forms of asbestos, or that some factor in addition to asbestos is necessary to cause the tumors.

Table 5-6 shows the distribution of cases by year of death and province in Canada to 1968. As malignant mesothelial tumors are difficult to diagnose, the tumor specimens in Canada were submitted to a review panel, and McDonald et al. (1973) reported on the review of 119 of 165 cases of mesothelioma reported between 1960 and 1968 in the Canadian National Survey. Based on histological observations only, the panel was in favor of the diagnosis for 50% of them, uncertain in 14%, and against diagnosis in 36%. A member of the U.K. British Mesothelioma Panel who viewed 44 of the 119 cases recorded essentially similar opinions. Twelve of 26 tumors (46%) were classified histologically as mixed cell type associated with asbestos exposure, compared with 8 of 73 (11%) classified as epithelial or mesenchymal. McDonald (1979a) reviewed all 254 cases of mesothelioma known in Quebec in the period 1960-1978. Twenty-one cases had been employed in the chrysotile mining industry, but, of these, five had been exposed to crocidolite in manufacturing gas mask pads in a small factory. Two of the other 16 may have been exposed to crocidolite which was processed at one of the mills for gas mask manufacture. Of importance were observations on residence. Four women had been exposed indirectly to chrysotile in the home, one man was the son of a miner and miller, and one other man was similarly exposed. Apart from these, only two persons with mesothelioma and two controls (secondary lung cancer) lived within 33 km of the chrysotile mines and mills.

Table 5-6. Distribution of mesothelial tumor cases by year of death and province (from McDonald *et al*. 1973).

Year	Ontario	Quebec	Other provinces	Canadian total
1960	-	6	9	15
1961	1	6	3	10
1962	4	4	5	13
1963	9	3	7	19
1964	6	8	3	17
1965	7	7	5	19
1966	8	14	9	31
1967	6	13	6	25
1968 (1st half)	5	9	2	16
	46	70	49	165
Incidence per million per annum (1960-1967)	0.8	1.5	0.9	1.0

5.4.2.2 Fiber Type and Mesothelioma

Because occupational experience suggests that different fiber types may carry different risks for the production of mesothelioma (possibly because of differences in physical dimensions), it is important to identify whether different fiber types are involved in the production of mesothelial tumors in the general population. The identification of fibers in tissue was not possible until the introduction of energy dispersive analytical techniques. While morphology and electron diffraction patterns were capable of distinguishing such asbestos fibers as serpentine or amphibole types, these analytical methods did not distinguish between individual fibrous amphibole types. In one study using an electron microscope, Pooley (1973b) examined lung parenchyma from 65 persons (26 with pleural and 7 with peritoneal mesothelioma) and 32 control cases matched for age and sex, and chosen at random, excluding cases with pulmonary tumors. The study showed that the most common fibers in the mesothelioma group were amphibole asbestos, whereas chrysotile was the predominant fiber type in the controls.

Studies of fiber type are under way in the United Kingdom, and a limited series has been examined in Canada in which individual fibers have been identified using energy dispersive techniques. Observations from the U.K. (Jones et al. 1980) showed that mesothelioma cases (86 studied) had more amphibole fibers in their lungs than did controls (29 cardiovascular disease and 27 bronchial carcinoma matched for place of death, age, and sex). Chrysotile fibers were not present in greater numbers in cases than in controls. Thirty cases had no chrysotile fibers in their lungs, and four mesothelioma cases had no amphibole fibers. Two of the latter had chrysotile and two had no detectable asbestos fibers. Analyses of lung tissues from 29 case-control pairs (mesothelioma - control with pulmonary metastases from a primary cancer other than lung cancer) from North America showed that there was a clear excess of amosite in cases, a marginal excess of crocidolite and tremolite in cases, and no difference for anthophyllite. The distribution of chrysotile in cases and controls was also remarkably similar (McDonald 1979b). The results of a very limited series of Canadian cases and controls (Gibbs and McDonald 1979) gave very similar results. Thus, the results of studies of fiber type in lung tissue suggest a consistent association between certain amphibole fibers (crocidolite and amosite) and mesothelioma. This is also consistent with the epidemiological evidence that the risk of mesothelioma after chrysotile exposure is considerably lower than after exposure to crocidolite or amosite.

The major difficulties in interpreting the results of fiber type are twofold. First, obtaining complete data as to the origin of the tissue specimens is a major difficulty. The distribution of fibers by type within the lung has not been adequately established, and because different sizes of fibers might migrate to different regions of the lung and pleura (Sebastien et al. 1977), this migration of fibers might, by size selection, give rise to differences in the types of fibers identified. Second, there is evidence that amphibole fibers remain in the lung somewhat longer than chrysotile fibers, and hence the absence of chrysotile in the lung may not totally eliminate the possibility that such fiber types were involved in mesothelioma production.

Whitwell et al. (1977) provided some useful data in assessing the likely risk of mesothelioma for the general population, although, unfortunately, the study was based on light optical methods which as shown by Sebastien et al. (1977) can underestimate fiber concentrations (see Table 5-2). Lung specimens from 88 persons who had been exposed to asbestos were examined. Seventy-three (83%) of the specimens contained 100,000 asbestos fibers per gram dried lung, and only one contained less than 20,000 fibers per gram. When asbestosis was present, lungs contained over 3 x 10^6 fibers per gram. In 100 control lungs (no industrial disease or lung cancer), there were less than 20,000 fibers per gram in 71% of specimens. Lungs from 100 persons with lung cancer but no industrial disease contained less than 20,000 fibers per gram dried lung in 80% of cases. The findings in the mesothelioma cases with various degrees of asbestosis showed geometric mean counts of 4.7 x 10^6, 9.6 x 10^6, and 28 x 10^6 fibers per gram dried lung for mild, moderate, and severe asbestosis, respectively. The study of housewives with limited exposure in a gas mask factory and case-control comparison were most revealing (see Table 5-7 and Figure 5-3). Mesothelioma appears to be related to relatively high exposures to asbestos, at least as reflected by optical counts. Fiber types and sizes which might be important were not determined. These findings are supported by the observations of Newhouse (1973) that the mesothelioma rate increased in asbestos factory workers with the severity and duration of asbestos exposures. As 95% of patients with mesothelioma in the Whitwell series had over 50,000 fibers per gram of dried lung (exposures, if short, must have been intense), the top 15% of the control series which had as many fibers might be considered at risk. Analyses of lung tissue from gas mask workers using electron microscopic methods have been reported by Jones et al. (1980), showing crocidolite concentrations to be high. Additional information is needed on the dimensions of fibers in lung tissue and on the pleura, as well as on differences in the retentions of the various fiber types.

5.4.3 LUNG FIBROSIS

The risks of lung and pleural fibrosis among persons occupationally exposed to all varieties of asbestos fibers have been well documented (IARC 1973). These effects are dose related, and suggest that risks in the working environment can be reduced to an extremely low level by appropriate environmental controls. Whether specific fiber sizes are more important in the production of asbestosis in humans is not known.

Table 5-7. Limited asbestos exposure in housewives leading to mesothelioma (from Whitwell *et al.* 1977).

Age at death (years)	Work	Duration of work (years)	Interval between first exposure and death (years)	Asbestos fiber count per gram dried lung
74	Sackware factory	1	60	287,000
78	"	1	60	555,000
59	"	2	30	300,000
47	"	3	30	3,300,000
55	Gas mask factory	5	30	57,000,000
61	"	4	31	23,000,000
57	"	0.5	30	17,000,000
69	"	0.5	35	1,600,000

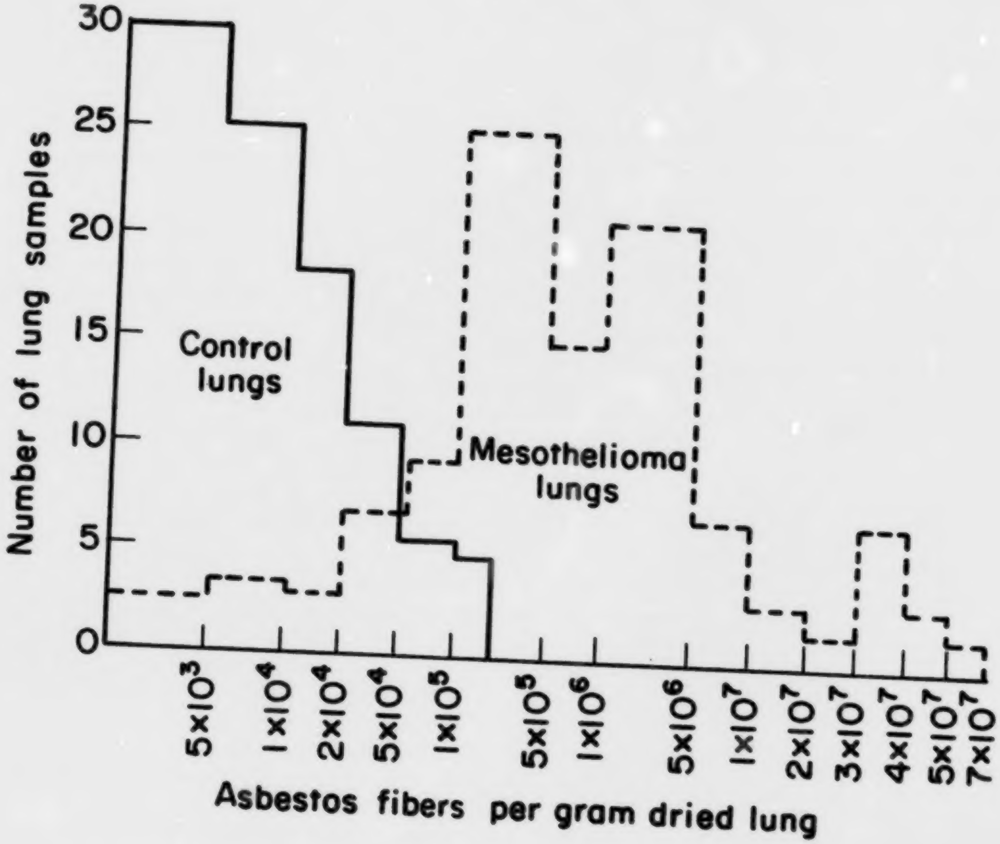

Figure 5-3. Comparison of asbestos fiber content of lungs from mesothelioma cases and normal control series (from Whitwell *et al.* 1977).

There is some evidence that increased rates of radiological change compatible with asbestosis can occur in persons living in households of workers (Rom et al. 1976; Anderson et al. 1979). The population studied was 679 household contacts of asbestos workers employed in a factory which produced amosite asbestos products from 1941 to 1954. The prevalence of radiographic abnormalities was significantly greater among household contacts than within a control population of urban New Jersey residents currently living in the same community as that in which the study population was identified.

It has also been shown that concentrations of airborne fibers in such homes may have been considerably greater than in the general environment. No cases of asbestosis have been reported in the general population, and comparisons of the levels of exposure which have produced the disease in the industry with those in the general environment indicate that there is probably a negligible risk of fibrosis of the lung at the concentrations of asbestos fiber present in ambient air.

It is perhaps important to note that lung fibrosis can occur in other industrial situations, for example, exposure to dusts which are not fibrous in appearance, such as crystalline silica which produces silicosis, and coal dust which produces coal miners' pneumoconiosis.

A recent study in Egypt (Noweir et al. 1980) suggested that the development of silicosis among workers exposed to silica-bearing dust was less likely if the workers' fathers had occupational histories of exposure to silica-bearing dust. Furthermore, this study suggested that workers with consanguinity in their family histories or with blood groups "O" or "AB" were more highly susceptible to the development of silicosis.

Talc produces talcosis, but the relative role played by the platy talc which is often contaminated with anthophyllite and tremolite fibers in situations where talcosis is found has not been fully determined.

Although long narrow glass fibers have been shown to produce fibrosis of the lung in experimental animals, there does not appear to be any evidence to date that these effects occur in humans exposed to man-made mineral fibers; however, this may be due to the dimensions of the fibers and possibly also to their durability and levels of exposure. Dodgson et al. (1979) reported nominal diameter sizes of glass and rock wool to be 6-15 μm. However, these contained a small proportion of small fibers (<3 μm), and some special fine fibers down to 1 μm in diameter or less have been produced since the 1940s in the U.S.A. and more recently in Europe (Hill 1977). Dodgson et al. (1979) reported thin respirable fiber concentrations in five man-made mineral fiber plants ranging in concentration from 0.004 to 0.027 fibers mL^{-1} in production and 0.023-0.129 fibers mL^{-1} in secondary processes. These concentrations are considerably below those normally encountered in asbestos production and manufacturing plants. Hill (1974) reported that common man-made mineral fiber products of the past contained similar amounts of respirable fiber to those present today.

More recently, nonasbestos-type fibers have received some attention. Hung et al. (1979) examined, by optical phase contrast, energy dispersive analysis, and electron microscopy, 20 naturally occurring mineral fibers, some of which are likely to be encountered in industry. They found that many of the dusts, when rendered airborne, contained fibers longer than 5 µm, were countable by the phase-contrast method, and had gross morphologies similar in certain respects to the asbestos minerals (see Table 5-5). Leineweber (1980) also examined a number of fibrous minerals, and drew attention to the need to consider not only fiber dimensions but also durability, both physical and biological, when assessing the potential hazard from nonasbestos fibers.

Bignon et al. (1979) reported on the characterization (crystallography, chemistry, size, and associated minerals) of some naturally occurring clay fibers and attapulgite fibers encountered in three drugs used as a treatment for gastrointestinal disease. Spanish attapulgite had diameters as small as 0.02-0.03 µm, and French attapulgite had a diameter of 0.2 µm. Attapulgite fibers were found at a concentration of 42,000 fibers mL^{-1} in the lung washing fluids recovered by bronchoalveolar lavage in a 41-year-old patient with lung fibrosis exposed for 3 years to attapulgite dusts during mining, milling, and processing attapulgite used for drug manufacture. The mean length, diameter, and aspect ratios were 1.5 µm, 0.11 µm, and 21, respectively. Attapulgite (Polygorskite) fibers were also found at a concentration of 300,000 mL^{-1} in the urine of a woman treated for 6 months with 9 $g.d^{-1}$ of a drug containing attapulgite. The results of these case studies indicate that other naturally occurring fibers may produce fibrosis, and epidemiological studies of populations exposed to other naturally occurring mineral fibers are needed to determine whether exposure to such fibers increases carcinogenic as well as fibrogenic risks.

5.4.4 LUNG CANCER

The association between occupational exposure to each of the varieties of asbestos and lung cancer has been well established (IARC 1973). The risk of lung cancer among chrysotile miners and among certain other occupational groups has been shown to be dose related (McDonald et al. 1974). Most researchers appear to accept the linear nature of this dose-response relationship, and attempts have been made to extrapolate to low doses. The major difficulty is that lung cancer arises from other causes such as smoking. Also, measurements of airborne fiber concentrations carried out in industry have been made only in recent years, and reflect only fibers greater than 5 µm in length having aspect ratios of 3 to 1 or greater. In the epidemiological studies in Canada, it has been necessary to convert past particle concentrations to equivalent fiber concentrations in order to assess the risk in relation to the present world-accepted methods of measuring airborne fibers (Walton et al. 1976). Similar conversions were necessary in the United Kingdom where airborne fibers were measured prior to 1962 using a different method from that currently used.

While the dose-response relationships are encouraging from the standpoint of establishing a relatively realistic standard for the control of lung cancer risks in the industrial setting, there are some differences in the lung cancer experience of different occupational groups and fiber types. A greater problem exists in extrapolating to the general population where concentrations of asbestos fibers will be orders of magnitude lower than in the industrial setting and where fiber sizes may be quite different from those inside industry. An attempt to provide information on the risks of lung cancer for the general population exposed to chrysotile asbestos is under way in Quebec. A pilot study has been conducted to determine the appropriate methodology for the measurement of airborne fiber concentrations in the Eastern Townships of Quebec around asbestos mines and mills and in control towns. Concentrations of electron microscopically visible fibers were found to be high (Gibbs et al. 1980). A preliminary analysis of mortality of persons living in areas around asbestos mines and in other parts of Quebec has been conducted for the period 1966-1977 by Pampalon et al. (1982). The mortality in the mining regions was examined in comparison with the experience of the general population of Quebec Province and was expressed as a standardized mortality ratio (SMR). There was an excess mortality among men which may largely be explained by the excesses associated with occupational exposure in the industry, as a high proportion of males in these mining towns worked in the mining industry. As far as women are concerned, there was no clear indication of any all-cause mortality excess or of mortality from certain causes among women in the asbestos towns. It is obviously important to examine in more depth the mortality among men in Thetford Mines and Asbestos, taking account of occupations, tobacco consumption, ethnic groups, and the migration between towns. Graham et al. (1977) found evidence of a slightly elevated incidence of digestive cancers among persons in counties where asbestos was mined. It is apparent that the studies of the persons living in areas such as Thetford Mines and Asbestos where definite air pollution from asbestos and other fibers have occurred are important; they can provide information on the real risk of malignancy for the general population exposed to chrysotile asbestos which, on the basis of existing data, is likely to be extremely low and probably undetectable when other factors such as smoking are taken into account.

Another study of importance in considering the risks for the general population from asbestos (amosite) in ambient air is that of

Hammond and Garfinkel (1980). The population studied lived within 1 km of an amosite factory which operated at Riverside between 1942 and 1954. A comparison population living in Totowa, a district which had similar socioeconomic status, race, national origin of inhabitants, and types of dwellings, was also chosen for study. Although no measurements of airborne fiber were available for the period when the factory operated, samples of settled dust collected from house and attics in the neighborhood contained appreciable numbers of amosite asbestos fibers. Hammond and Garfinkel (1980) considered it safe to assume that people living in the neighborhood were exposed to amosite, but that exposures were extremely light in comparison with those of men working in the factory. Between January 1, 1962, and December 31, 1976, 780 (43.8%) of Riverside subjects and 1735 (46%) of the Totowa subjects had died. Cancer (all sites) accounted for 163 (9.2%) of the Riverside subjects and 353 (9.4%) of deaths of the Totowa subjects. Lung cancer accounted for 41 (2.3%) of deaths in Riverside and 98 (2.6%) of deaths in Totowa. Both lung cancer and colorectal cancer mortalities were slightly higher in Totowa than in Riverside, and the number of deaths from other sites were small. One death from pleural mesothelioma occurred in a Riverside subject. Whether this person was occupationally exposed to asbestos is not known. This death occurred relatively early (1966) in the follow-up, which would mean a relatively short period from first exposure if neighborhood exposure was involved.

Thus two residential studies, one concerned with chrysotile and the other with amosite, suggest that the cancer risks for the general population from environmental exposure are slight or undetectable. In contrast, exposures in the households of workers can be very important. Similar studies of populations environmentally exposed and domestically exposed are needed to confirm these observations and to put the risks of cancer and fibrosis for the general public due to exposure to the various fiber types in perspective. Control of asbestos exposure in the work place is essential, and attention should be directed towards nonasbestos fibers which have physical characteristics similar to those of asbestos fibers, especially where exposures have been high. There is no evidence of health effects in the general population which have been linked to platy particles, and only recently has attention become focused on nonasbestos fibers in tissues and ambient air.

Recently, the mortality experience of employees in 13 man-made mineral fiber production plants in seven European countries was reported (Simonato et al. 1982). Cancer incidence rates were also available for nine plants in four countries. No unusual mortality or cancer incidence was found in comparison with the general population. However, there was a twofold excess of lung cancer deaths after 30 years or more since first exposure. In another mortality study in Italy (Bertazzi et al. 1982), there was also an indication that malignancies were in excess when compared with national and regional rates.

GLOSSARY

agglomerate - two or more particles held together by relatively weak cohesive forces

aggregate - particle or assembly of particles held together by strong inter- or intramolecular or atomic cohesive forces

alveolus - an air cell of the lungs

amphibole - any of a group of minerals $A_2B_5(Si, Al)_8O_{22}(OH)_2$

atrium - (in the lung) a subdivision of the alveolar duct from which alveolar sacs open

bifurcation - the division of the trachea into the right and left main bronchi

bronchiole - a minute thin-walled branch of a bronchus

bronchiolitis - inflammation of the mucous membrane of the bronchiole

bronchus - either of the two primary divisions of the trachea that lead respectively into the right and the left lung

buccal - relating to the cheeks or the cavity of the mouth

carcinogen - a substance or agent producing or inciting cancer

carina trachea - the ridge separating the openings of the right and left main bronchi at their junction with the trachea

chrysotile - a mineral consisting of a fibrous silky serpentine and constituting a kind of asbestos

crocidolite - a mineral of the amphibole group that occurs in silky fibers

dead space - the portion of the respiratory system which is external to the bronchioles and through which air must pass to reach the bronchioles and alveoli

endocytosis - incorporation of substances into a cell by phagocytosis or pinocytosis (the uptake of fluid by a cell by invagination and pinching off of the cell membrane)

epiglottis - a thin plate of flexible cartilage that folds back over and protects the glottis during swallowing ferruginous - containing iron

fibrosis - a condition marked by increase of interstitial fibrous tissue

fume fever - acute disability of short duration which occurs when fume is inhaled from a metal heated to a temperature above its melting point; symptoms include nausea, thirst, headache, pain in limbs, and exhaustion

inguinal - situated in the region of the groin or in either of the lowest lateral regions of the abdomen

intercostal - situated between the ribs

lumbar - relating to the loins or the vertebrae between the thoracic vertebrae and sacrum

lymphangitis - inflammation of the walls of the lymphatic vessels

macrophage - a large phagocyte

mediastinum - an irregular median septum of the thoracic cavity formed of the opposing medial walls of the parietal pleura that encloses the thoracic viscera except the lungs

mesenchyme - a loosely organized mesodermal connective tissue giving rise to such structures as connective tissues, blood, lymphatics, bone, and cartilage

mesothelium - epithelium derived from mesoderm that lines the body cavity of a vertebrate embryo and gives rise to epithelia, striated and heart muscle, and several minor structures

mesothelioma - a tumor derived from mesothelial tissue (as that lining the peritoneum or pleura)

morning fever (or reaction) - acute illness consisting of fever, myalgia cough, tightness in the chest, and breathlessness on exertion which usually resolves in 24 h. Symptoms are worse at the beginning of a working week and improve during the rest of the week, but recur on reexposure after an absence from work

nasal vestibule - the anterior part of the nasal cavity

nasopharyngeal - relating to the nose and pharynx

oropharynx - the oral pharynx, located between the lower border of the soft palate and the larynx

parietal - forming the upper posterior wall of the head periarterial - surrounding the artery

peritoneum - the smooth transparent serous membrane that lines the cavity of the abdomen of a mammal and is reflected inward over the abdominal and pelvic viscera

phagocyte - a cell (e.g. a leukocyte) that characteristically engulfs foreign materials

phagocytosis - the engulfing and usual destruction of particulate matter by phagocytes

phagosome - a membrane-surrounded vesicle that encloses materials taken into the cell by endocytosis

pharynx - the part of the vertebrate alimentary canal between the cavity of the mouth and the esophagus

pleura - the delicate serous membrane that lines each half of the thorax of mammals and is folded back over the surface of the lung of the same side

recruitable macrophages - phagocytic cells contained in the alveolar surface epithelium

scintigram - a two-dimensional picture of a bodily radiation source obtained by the use of radioisotopes

serous - relating to or resembling serum

serpentine - a mineral consisting essentially of a hydrous magnesium silicate $Mg_3Si_2O_7.2H_2O$

Silastic - a trade name for any of several heat-resistant silicone rubbers

streamline - the path of a fluid particle relative to a solid body past which the fluid is moving in smooth flow without turbulence

subserosal - situated or occurring beneath a (usually) enclosing serous membrane

thermophoresis - the movement of particles within the lung in response to differential heat patterns

trachea - the main trunk of the system of tubes by which air passes to and from the lung in vertebrates

tracheobronchial - relating to both trachea and bronchi

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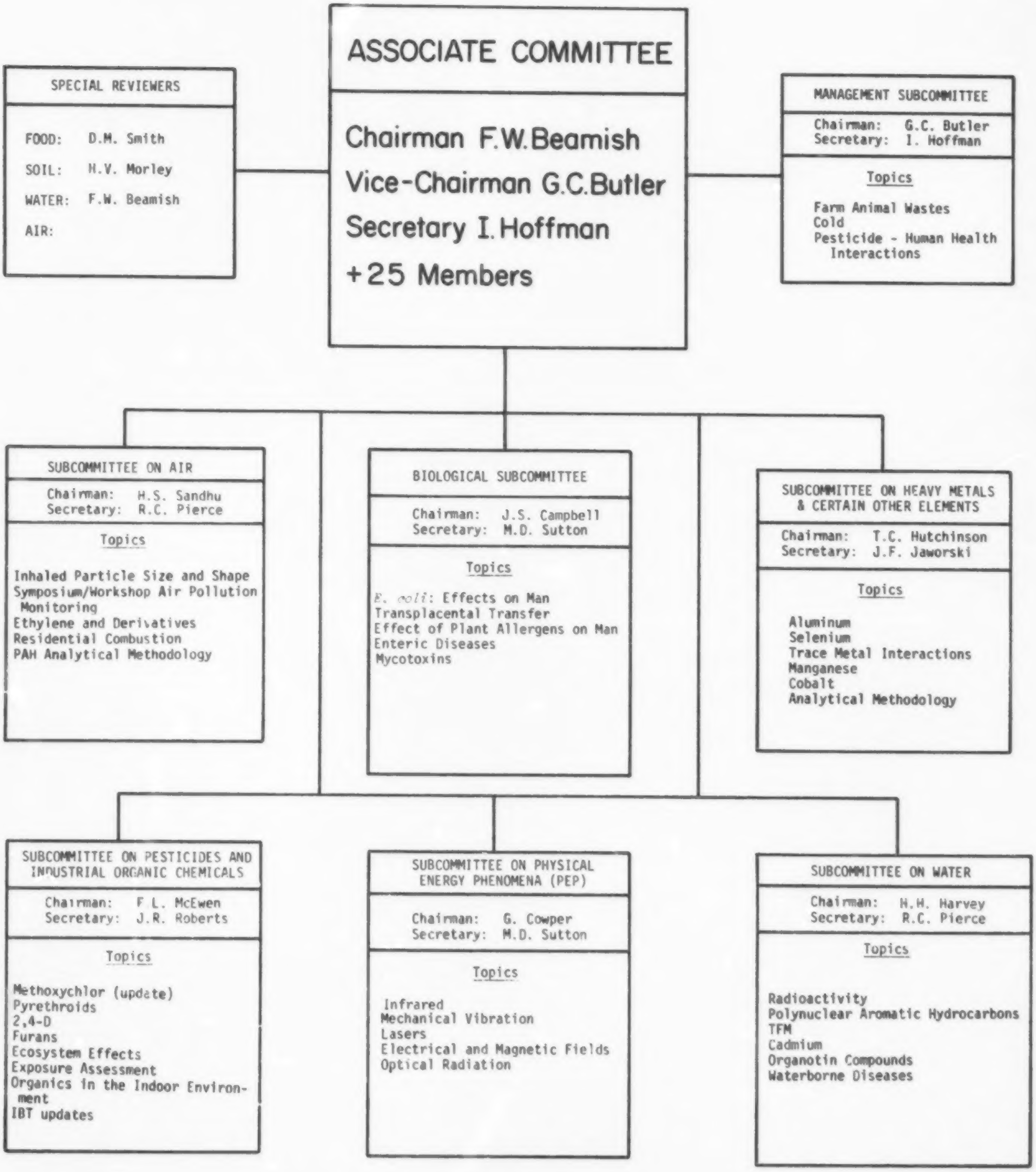

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